JC07 Rec'd PCT/PTO 14 MAY 2001

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER: P6656US0
		US APPLICATION NO (if known, see 37 CFR 1.5): 09/831754
INTERNATIONAL APPLICATION NO.: PCT/EP99/08744	INTERNATIONAL FILING DATE: 12 November 1999	PRIORITY DATE CLAIMED: 12 November 1998

TITLE OF INVENTION: METHODS OF DIAGNOSING OR TREATING NEUROLOGICAL DISEASES AND CELL DEGENERATION

APPLICANT(S) FOR DO/EO/US: Roger NITSCH and Isabell GREEVE

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    International Search Report - EPO
    PCT/IB/301 Form
    PCT/IB/304 Form
    PCT/IB/306 Form
    PCT/IB/308 Form
    First Page of Publication
    International Preliminary Examination Report - with no annexes
    Sequence Listing

US APPLICATION NO.(if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/831754	PCT/EP99/08744	P66566US0

	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) . . $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . $710.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) **$1000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$860.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☒ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**38** - 20 =	-18-	x $18.00	$ 324.00	
Independent Claims	**14** - 3 =	-11-	x $80.00	$ 880.00	
Multiple Dependent Claim(s) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 2194.00	
Reduction by 1/2 for filing by **small entity**, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 2194.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 2194.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$	
TOTAL FEES ENCLOSED =				$ 2194.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 2194.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ ____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO:

JACOBSON HOLMAN PLLC
400 7th Street, N.W., Suite 600
Washington, DC 20004
202-638-6666
CUSTOMER NUMBER: 00136

By _____
William E. Player
Reg. No. 31,409

JPH&S 3/95

#4

PRIORITY Rec'd 15 OCT 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Roger NITSCH et al.

Serial No.: 09/831,754 Group Art Unit: Unassigned

Filed: May 14, 2001 Examiner: Unassigned

For: METHODS OF DIAGNOSING OR TREATING NEUROLOGICAL DISEASES AND CELL DEGENERATION

AMENDMENT

Commissioner of Patents
Washington, DC 20231

Sir:

Applicants submit the instant Amendment in conjunction with the Sequence listing submitted concurrently herewith.

IN THE SPECIFICATION

Replace the originally filed Sequence Listing with the Sequence Listing (pages 1-8) submitted concurrently herewith.

By the instant Amendment, the Sequence Listing filed, concurrently herewith, is added to the specification.

Favorable action is requested..

Respectfully submitted,

JACOBSON HOLMAN PLLC

By: _____
William E. Player
Registration No. 31,409

Date: October 15, 2001

400 Seventh Street, N.W.
Washington, DC 20004
(202) 638-6666
Atty. Dkt. No.: P66566US0
WEP/vjb
R:\HOME\VBYERS\2001\October\P66566US0-Seq List Amdt.wpd

43. An isolated DNA molecule capable of hybridizing with the complement of the cDNA described in SEQ ID NO: 2 under stringent condition.

44. An isolated DNA molecule of claim 43 encoding a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

45. An isolated nucleic acid molecule of claim 40 encoding a protein molecule, the function of which is to protect cells of the nerve system, muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, lung, trachea or placenta against degeneration and/or cell death.

46. A vector comprising a nucleic acid molecule according to claim 39.

47. A vector according to claim 46 wherein said vector is a plasmid, a virus or a bacteriophage.

48. A plasmid according to claim 47 wherein said plasmid is adapted for expression in a yeast cell and further comprises the regulatory elements necessary for expression of said nucleic acid molecule.

49. A plasmid according to claim 47 wherein said plasmid is adapted for expression in a bacterial cell and further comprises the regulatory elements necessary for expression of said nucleic acid molecule.

50. A plasmid according to claim 46 wherein said plasmid is adapted for expression in a mammalian cell and further comprises the regulatory elements necessary for expression of said nucleic acid molecule.

51. A cell transformed with a nucleic acid molecule according to claim 39, wherein said cell is in particular a bacterial cell, a yeast cell, a mammalian cell, or an insect cell.

52. A protein molecule shown in SEQ ID NO:1.

53. A protein molecule, the function of which is to protect cells against degeneration and/or cell death, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof.

54. A protein molecule of claim 52, the function of which is to protect cells of the nerve system, muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, against degeneration and/or cell death.

55. An antibody specifically immunoreactive with an immunogen, wherein said immunogen is a protein molecule shown in SEQ ID NO: 1.

56. An antibody specifically immunoreactive with a protein molecule, the function of which is to protect cells against degeneration and/or cell death, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO: 1 or a functional variant thereof.

57. A method of detecting pathological cells in a subject which comprises immunocyto-chemically staining cells with an antibody of claim 55, wherein a low degree of staining in said cell compared to a cell representing a known health status indicates a pathological change of said cells.

58. A method of claim 57, wherein cells of the nerve system, muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, lung, trachea or placenta are used.

59. A method of diagnosing or prognosing a disease, in particular a neurological disease, in a subject comprising:

a) determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

i) a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

ii) a transcription product of a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iii) a protein molecule wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iv) a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

v) a transcription product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vi) a translation product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vii) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

viii) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f), and

b) comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby diagnosing or prognosing a disease, in particular a neurological disease, in said subject.

60. A method of monitoring the progression of a disease, in particular a neurological disease, in a subject, comprising:

a) determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

i) a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

ii) a transcription product of a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iii) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iv) a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

v) a transcription product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vi) a translation product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vii) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

viii) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f), and

b) comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby monitoring progression of a disease, in particular a neurological disease, in said subject.

61. A method of evaluating a treatment for a disease, in particular a neurological disease, in a subject, said method comprising:

a) determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

i) a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

ii) a transcription product of a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iii) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iv) a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

v) a transcription product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vi) a translation product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vii) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

viii) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f), and

b) comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby monitoring progression of a disease, in particular a neurological disease, in said subject.

62. The method according to claim 59, wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

63. The method according to claim 59, wherein a decrease of a level or an activity of (i) a transcription product of a DNA molecule encoding a protein molecule, the amino acid sequence of which comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof or (ii) a protein molecule, the amino acid sequence of which comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof, in a sample from said subject relative to a reference value representing a known health status indicates the presence of a disease, in particular a neurological disease, in said subject.

64. The method according to claim 59, wherein said DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

65. The method according to claim 59, wherein said subject suffers from Alzheimer's disease or related neurofibrillary disorders, or neurodegenerative states characterized by cell

degeneration or cell death, or Parkingson's disease, or Huntington disease, or Amyotrophic lateralsclerosis or Pick's disease.

66. An agent which affects an activity, or level, or both said activity and level, of at least one substance which is selected from the group consisting of

a) a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

b) a transcription product of a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

d) a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

e) a transcription product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

f) a translation product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f), and

i) comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby monitoring progression of a disease, in particular a neurological disease, in said subject.

67. An agent of claim 66, wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

68. An agent of claim 66 wherein said DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

69. A medicament comprising an agent according to claim 66.

70. Use of an agent for preparation of a medicament for treating or preventing a neurological disease, in particular Alzheimer's disease, which agent affects an activity, or level, or both said activity and level, of at least one substance which is selected from the group consisting of

a) a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

b) a transcription product of a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

d) a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

e) a transcription product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

f) a translation product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f), and

i) comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby monitoring progression of a disease, in particular a neurological disease, in said subject.

71. Use of an agent according to claim 70, wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

72. Use of an agent according to claim 70, wherein said DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

73. A method of identifying an agent that affects an activity, or level, or both said activity and level, of at least one substance, said method comprising the steps of:

a) providing a sample containing at least one substance selected from the group consisting of

i) a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

ii) a transcription product of a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iii) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iv) a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

v) a transcription product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vi) a translation product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vii) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

viii) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f), and

b) contacting said sample with at least one agent,

c) comparing an activity, or level, or both said activity and level, of at least one of said substances before and after contacting.

74. A method of claim 73 wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

75. A method of claim 73 wherein said DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

76. A kit for diagnosis, or prognosis of a disease, said kit comprising:

a) at least one reagent which is selected from the group consisting of reagents that selectively detect

i) a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

ii) a transcription product of a DNA molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iii) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO:1 or a functional variant thereof,

iv) a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

v) a transcription product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vi) a translation product of a DNA molecule capable of hybridizing with the complement of the DNA described in SEQ ID NO: 2 under stringent conditions,

vii) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

viii) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f), and

b) instructions for diagnosing or prognosing said disease by

i) detecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) in a sample from said subject; and

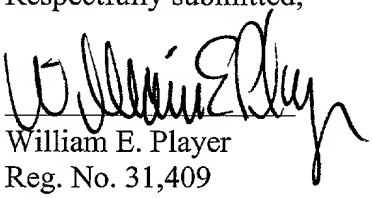
ii) diagnosing, or prognosing said disease, wherein a varied level, or activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) similar or equal to a reference value representing a known disease status indicates diagnosis, or prognosis of said disease.

REMARKS

New claims 39-76 are presented for consideration. Claims 39-76 correspond to original claims 1-38, revised to eliminate multiple dependencies and to, otherwise, more clearly define the instant invention.

Favorable action is requested.

Respectfully submitted,

By: 

William E. Player
Reg. No. 31,409

JACOBSON HOLMAN PLLC400
Seventh Street, N.W.
The Jenifer Building
Washington, D.C. 20004
Tel.: (202) 638-6666
Atty. Dkt. No.: P66566US0
G:\SHARED\P66566preamd wpd

ATTY. DOCKET NO.: P66566US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Roger NITSCH et al.

Serial No.: 09/831,754 Group Art Unit: Unassigned

Filed: May 14, 2001 Examiner: Unassigned

For: METHODS OF DIAGNOSING OR TREATING NEUROLOGICAL DISEASES AND CELL DEGENERATION

RESPONSE TO NOTICE TO COMPLY WITH SEQUENCE RULES

Commissioner of Patents
Washington, D.C. 20231

Sir:

In accordance with the Notice to Comply with sequence rules 37 CFR 1.821 – 1.825, a copy of which is attached, hereto, applicant submits, herewith a substitute:

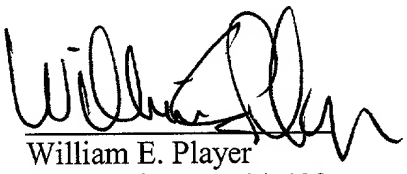
(1) Computer Readable Form (CRF) of Sequence Listing; and

(2) Substitute paper copy of Sequence Listing.

The content of the computer readable form and the paper copy are the same and, where applicable, include no new matter, as required by 37 CFR § 1.821(e), § 1.821(f), § 1.821(g), § 1.825(b), or 1.825(d).

Favorable action is requested.

Respectfully submitted,

By 
William E. Player
Registration No. 31,409

Date: October 15, 2001

JACOBSON HOLMAN PLLC
400 Seventh Street, N.W.
Washington, D.C. 20004
Telephone: (202) 638-6666
Atty. Docket No.: P66566US0
WEP/vjb
R:\HOME\VBYERS\2001\October\P66566US0-Resp to Not to Comply wpd

SEQUENCE LISTING

<110> Nitsch, Roger

<120> Methods of diagnosing or treating neurological diseases and cell degeneration

<130> Nitsch PCT/EP 99/08744

<140>
<141>

<150> PCT/EP 99/08744
<151> 1999-11-12

<160> 4

<170> PatentIn Ver. 2.1

<210> 1
<211> 516
<212> PRT
<213> Homo sapiens

<400> 1

```
Met Glu Pro Ala Val Ser Leu Ala Val Cys Ala Leu Leu Phe Leu Leu
  1               5                  10                  15

Trp Val Arg Leu Lys Gly Leu Glu Phe Val Leu Ile His Gln Arg Trp
             20                  25                  30

Val Phe Val Cys Leu Phe Leu Leu Pro Leu Ser Leu Ile Phe Asp Ile
         35                  40                  45

Tyr Tyr Tyr Val Arg Ala Trp Val Val Phe Lys Leu Ser Ser Ala Pro
     50                  55                  60

Arg Leu His Glu Gln Arg Val Arg Asp Ile Gln Lys Gln Val Arg Glu
 65                  70                  75                  80

Trp Lys Glu Gln Gly Ser Lys Thr Phe Met Cys Thr Gly Arg Pro Gly
                 85                  90                  95

Trp Leu Thr Val Ser Leu Arg Val Gly Lys Tyr Lys Lys Thr His Lys
            100                 105                 110

Asn Ile Met Ile Asn Leu Met Asp Ile Leu Glu Val Asp Thr Lys Lys
        115                 120                 125
```

```
Gln Ile Val Arg Val Glu Pro Leu Val Thr Met Gly Gln Val Thr Ala
    130                 135                 140

Leu Leu Thr Ser Ile Gly Trp Thr Leu Pro Val Leu Pro Glu Leu Asp
145                 150                 155                 160

Asp Leu Thr Val Gly Gly Leu Ile Met Gly Thr Gly Ile Glu Ser Ser
                165                 170                 175

Ser His Lys Tyr Gly Leu Phe Gln His Ile Cys Thr Ala Tyr Glu Leu
            180                 185                 190

Val Leu Ala Asp Gly Ser Phe Val Arg Cys Thr Pro Ser Glu Asn Ser
        195                 200                 205

Asp Leu Phe Tyr Ala Val Pro Trp Ser Cys Gly Thr Leu Gly Phe Leu
    210                 215                 220

Val Ala Ala Glu Ile Arg Ile Ile Pro Ala Lys Lys Tyr Val Lys Leu
225                 230                 235                 240

Arg Phe Glu Pro Val Arg Gly Leu Glu Ala Ile Cys Ala Lys Phe Thr
                245                 250                 255

His Glu Ser Gln Arg Gln Glu Asn His Phe Val Glu Gly Leu Leu Tyr
            260                 265                 270

Ser Leu Asp Glu Ala Val Ile Met Thr Gly Val Met Thr Asp Glu Ala
        275                 280                 285

Glu Pro Ser Lys Leu Asn Ser Ile Gly Asn Tyr Tyr Lys Pro Trp Phe
    290                 295                 300

Phe Lys His Val Glu Asn Tyr Leu Lys Thr Asn Arg Glu Gly Leu Glu
305                 310                 315                 320

Tyr Ile Pro Leu Arg His Tyr Tyr His Arg His Thr Arg Ser Ile Phe
                325                 330                 335

Trp Glu Leu Gln Asp Ile Ile Pro Phe Gly Asn Asn Pro Ile Phe Arg
            340                 345                 350

Tyr Leu Phe Gly Trp Met Val Pro Pro Lys Ile Ser Leu Leu Lys Leu
        355                 360                 365

Thr Gln Gly Glu Thr Leu Arg Lys Leu Tyr Glu Gln His His Val Val
    370                 375                 380
```

Gln Asp Met Leu Val Pro Met Lys Cys Leu Gln Gln Ala Leu His Thr
385   390   395   400

Phe Gln Asn Asp Ile His Val Tyr Pro Ile Trp Leu Cys Pro Phe Ile
                405   410   415

Leu Pro Ser Gln Pro Gly Leu Val His Pro Lys Gly Asn Glu Ala Glu
            420   425   430

Leu Tyr Ile Asp Ile Gly Ala Tyr Gly Glu Pro Arg Val Lys His Phe
        435   440   445

Glu Ala Arg Ser Cys Met Arg Gln Leu Glu Lys Phe Val Arg Ser Val
    450   455   460

His Gly Phe Gln Met Leu Tyr Ala Asp Cys Tyr Met Asn Arg Glu Glu
465   470   475   480

Phe Trp Glu Met Phe Asp Gly Ser Leu Tyr His Lys Leu Arg Glu Lys
                485   490   495

Leu Gly Cys Gln Asp Ala Phe Pro Glu Val Tyr Asp Lys Ile Cys Lys
            500   505   510

Ala Ala Arg His
        515

<210> 2
<211> 4248
<212> DNA
<213> Homo sapiens

<400> 2
cccgggctgt gggctacagg cgcagagcgg gccaggcgcg gagctggcgg cagtgacagg 60
aggcgcgaac ccgcagcgct taccgcgcgg cgccgcacca tggagcccgc cgtgtcgctg 120
gccgtgtgcg cgctgctctt cctgctgtgg gtgcgcctga aggggctgga gttcgtgctc 180
atccaccagc gctgggtgtt cgtgtgcctc ttcctcctgc cgctctcgct tatcttcgat 240
atctactact acgtgcgcgc ctgggtggtg ttcaagctca gcagcgctcc gcgcctgcac 300
gagcagcgcg tgcgggacat ccagaagcag gtgcgggaat ggaaggagca gggtagcaag 360
accttcatgt gcacggggcg ccctggctgg ctcactgtct cactacgtgt cgggaagtac 420
aagaagacac acaaaaacat catgatcaac ctgatggaca ttctggaagt ggacaccaag 480
aaacagattg tccgtgtgga gcccttggtg accatgggcc aggtgactgc cctgctgacc 540
tccattggct ggactctccc cgtgttgcct gagcttgatg acctcacagt gggggcttg 600
atcatgggca caggcatcga gtcatcatcc cacaagtacg gcctgttcca acacatctgc 660
actgcttacg agctggtcct ggctgatggc agctttgtgc gatgcactcc gtccgaaaac 720

tcagacctgt tctatgccgt accctggtcc tgtgggacgc tgggtttcct ggtggccgct 780
gagatccgca tcatccctgc caagaagtac gtcaagctgc gtttcgagcc agtgcggggc 840
ctggaggcta tctgtgccaa gttcacccac gagtcccagc ggcaggagaa ccacttcgtg 900
gaagggctgc tctactccct ggatgaggct gtcattatga caggggtcat gacagatgag 960
gcagagccca gcaagctgaa tagcattggc aattactaca agccgtggtt ctttaagcat 1020
gtggagaact atctgaagac aaaccgagag ggcctggagt acattccctt gagacactac 1080
taccaccgcc acacgcgcag catcttctgg gagctccagg acatcatccc ctttggcaac 1140
aaccccatct tccgctacct ctttggctgg atggtgcctc ccaagatctc cctcctgaag 1200
ctgacccagg gtgagaccct gcgcaagctg tacgagcagc accacgtggt gcaggacatg 1260
ctggtgccca tgaagtgcct gcagcaggcc ctgcacacct tccaaaacga catccacgtc 1320
taccccatct ggctgtgtcc gttcatcctg cccagccagc caggcctagt gcaccccaaa 1380
ggaaatgagg cagagctcta catcgacatt ggagcatatg gggagccgcg tgtgaaacac 1440
tttgaagcca ggtcctgcat gaggcagctg gagaagtttg tccgcagcgt gcatggcttc 1500
cagatgctgt atgccgactg ctacatgaac cgggaggagt tctgggagat gtttgatggc 1560
tccttgtacc acaagctgcg agagaagctg ggttgccagg acgccttccc cgaggtgtac 1620
gacaagatct gcaaggccgc caggcactga gctggagccc gcctggagag acagacacgt 1680
gtgagtggtc aggcatcttc ccttcactca agcttggctg ctttcctaga tccacacttt 1740
caaagagaaa cccctccaga actcccaccc tgacagccca acaccacctt cctcctggct 1800
tccaggggggc agcccagtgg aatggaaaga atgtgggatt tggagtcaga caagcctgag 1860
tccagttccc cgtttagaac tcattagctg tgtgactctg ggtgagtccc ttaacccctc 1920
tgagcccggg tctcttcatt agttgaaagg gatagtaata cctacttgca ggttgttgtc 1980
atctgagttg agcactggtc acattgaagg tgctgggtaa gtggtagctc ttgttgcttc 2040
ccgttcagcg tcacatctgc agtggagcct gaaaaggctc cacattaggt cacctgtgca 2100
cagccatggc tggaatgatg aaggggatac gctggagttg ccctgccatc gcctccatca 2160
gccagacgag gtcctcacag gagaaggaca gctcttcccc accctgggat ctcaggaggg 2220
cagccacgga gtggggaggc cccagatgcg ctgtgccaaa gccaggtccg aggccaaagt 2280
tctccctgcc atccttggtg ccgtcctgcc ccttcctcct tcatgcctgg gcctgcaggc 2340
ccaccccagc caccactgag tccactcgga gtgccctgtg ttcctggaga aggcattcca 2400
gggttgaatc ttgtcccagc ctcagcctgg gacacctagg tggagagagt ggtctccgct 2460
ctgaattgga tccaggggac ctgggctcat tcttcttggc tcaccaaccc tgcaggcctc 2520
atctttccca aaacccactt tgtcttggtg ggagtgggtc cgcgctgctc tgcagcaggg 2580
gctggggagt ggacagcatc aggtgggaaa gtggagtcca ccctcatgtt tctgtaggat 2640
tctcaccgtg gggctggaag aaaagagcat cgacttgatt tctccaacca ctcatccctc 2700
tttttctttc ttccaccact ccccacccca gctgtagtta atttcagtgc cttacaaatc 2760
ctaagctcag agaaagttcc atttccgttc cagagggaag ggaacctccc taggtccttc 2820
cctggcttgt tataacgcaa agcttggttg tttatgcaac tctatcttaa gaactgccca 2880
gcctcagctg aaaacccgaa tctgagaagg aattgcgtca tgtaagggaa gctggaatta 2940
agggagctga gccagtcatg gttgtggcgt gtgagtcagg agacctaggt ttcagcccct 3000
ctctactgtc agcgagctgt gcaacgtggg caagtcattg tcctctgagc tgcagtttcc 3060
tcatctgtca catcgctaca gacaagacct ccctggaacc cttctgattg tcttagacac 3120
tgtggttgca aaacccacgg aaagcctcat ttgtgtggaa agtcagagga aaaatgatcc 3180
agtggacact tggggattat ctgtcattca agatccttcc ttcaacccca aggccagctc 3240
ccatctcatt tccagaaagg ctcatacctg gcttgcaggg aagcatctgt cttgtcattc 3300
caggtgccag aatcctctca gagtcattga agggtgttca cccatcccac ccaaggcttg 3360
gcacactgcc agtgtcttag cagggtcttg tgagggctgg gggcatccag gcactcagaa 3420
ggcaaaggaa ccaccctacc catttggcct ctggaggggg cagaagaaag aaagaaacct 3480
catcctatat tttacaaagc atgtgaattc tggcattagc tctcatagga gacccatgtg 3540
cttccttgct cagtgcaaaa ctgatgattc tacttgctgt agatgaatgg ttaacacgag 3600

ctagttaaac agtgccattg ttttgccagt gaagcctcca accctaagcc actgggacgg 3660
tggccagaga tgccagcagc ctctgtcgcc cttagtcata taaccaaaat ccagacctta 3720
tccacaaccc ggggcttgga aaggaaggta ttttggaatc acaccctccg gttatgttgc 3780
tccagtaaaa tcttgcctgg aaagaggcag tcttcttagc atggtgagct gagttcatgg 3840
ctttttttg tagccagtcc tgtccctggc catccatgtg atggttttgg atggagttaa 3900
acttgatgcc agtgggcagt gcatgtggaa agtatcagag taagcctctc ccctccagag 3960
ccctgagttt cttggctgca tgaaggtttt ctttagaatc agaattgtag ccagtttctt 4020
tggccagaag gatgaatact tggatattac tgaaagggag gggtggagat gggtgtggca 4080
gtgtatggtg tgtgattttt attttcttct ttggtcatgg gggccaagga gaaaggcatg 4140
aatcttccct gtcaggctct tacagccaca ggcactgtgt ctactgtctg gaagacatgt 4200
ccccgtggct gtggggccgc tgcttctgtt taaataaaag tggcctgg 4248

<210> 3
<211> 4187
<212> DNA
<213> Homo sapiens

<400> 3
ggcgcgaacc cgcagcgctt accgcgcggc gccgcaccat ggagcccgcc gtgtcgctgg 60
ccgtgtgcgc gctgctcttc ctgctgtggg tgcgcctgaa ggggctggag ttcgtgctca 120
tccaccagcg ctgggtgttc gtgtgcctct tcctcctgcc gctctcgctt atcttcgata 180
tctactacta cgtgcgcgcc tgggtggtgt tcaagctcag cagcgctccg cgcctgcacg 240
agcagcgcgt gcgggacatc cagaagcagg tgcgggaatg gaaggagcag ggtagcaaga 300
ccttcatgtg cacggggcgc cctggctggc tcactgtctc actacgtgtc gggaagtaca 360
agaagacaca caaaaacatc atgatcaacc tgatggacat tctggaagtg gacaccaaga 420
aacagattgt ccgtgtggag cccttggtga ccatgggcca ggtgactgcc ctgctgacct 480
ccattggctg gactctcccc gtgttgcctg agcttgatga cctcacagtg gggggcttga 540
tcatgggcac aggcatcgag tcatcatccc acaagtacgg cctgttccaa cacatctgca 600
ctgcttacga gctggtcctg gctgatggca gctttgtgcg atgcactccg tccgaaaact 660
cagacctgtt ctatgccgta ccctggtcct gtgggacgct gggtttcctg gtggccgctg 720
agatccgcat catccctgcc aagaagtacg tcaagctgcg tttcgagcca gtgcggggcc 780
tggaggctat ctgtgccaag ttcacccacg agtcccagcg gcaggagaac cacttcgtgg 840
aagggctgct ctactccctg gatgaggctg tcattatgac aggggtcatg acagatgagg 900
cagagcccag caagctgaat agcattggca attactacaa gccgtggttc tttaagcatg 960
tggagaacta tctgaagaca aaccgagagg gcctggagta cattcccttg agacactact 1020
accaccgcca cacgcgcagc atcttctggg agctccagga catcatcccc tttggcaaca 1080
accccatctt ccgctacctc tttggctgga tggtgcctcc caagatctcc ctcctgaagc 1140
tgacccaggg tgagaccctg cgcaagctgt acgagcagca ccacgtggtg caggacatgc 1200
tggtgcccat gaagtgcctg cagcaggccc tgcacacctt ccaaaacgac atccacgtct 1260
accccatctg gctgtgtccg ttcatcctgc ccagccagcc aggcctagtg caccccaaag 1320
gaaatgaggc agagctctac atcgacattg gagcatatgg ggagccgcgt gtgaaacact 1380
ttgaagccag gtcctgcatg aggcagctgg agaagtttgt ccgcagcgtg catggcttcc 1440
agatgctgta tgccgactgc tacatgaacc gggaggagtt ctgggagatg tttgatggct 1500
ccttgtacca caagctgcga gagaagctgg gttgccagga cgccttcccc gaggtgtacg 1560
acaagatctg caaggccgcc aggcactgag ctggagcccg cctggagaga cagacacgtg 1620
tgagtggtca ggcatcttcc cttcactcaa gcttggctgc tttcctagat ccacactttc 1680
aaagagaaac ccctccagaa ctcccaccct gacagcccaa caccaccttc ctcctggctt 1740

ccaggggggca gcccagtgga atggaaagaa tgtgggattt ggagtcagac aagcctgagt 1800
ccagttcccc gtttagaact cattagctgt gtgactctgg gtgagtccct taacccctct 1860
gagcccgggt ctcttcatta gttgaaaggg atagtaatac ctacttgcag gttgttgtca 1920
tctgagttga gcactggtca cattgaaggt gctgggtaag tggtagctct tgttgcttcc 1980
cgttcagcgt cacatctgca gtggagcctg aaaaggctcc acattaggtc acctgtgcac 2040
agccatggct ggaatgatga aggggatacg ctggagttgc cctgccatcg cctccatcag 2100
ccagacgagg tcctcacagg agaaggacag ctcttcccca ccctgggatc tcaggagggc 2160
agccacggag tggggaggcc ccagatgcgc tgtgccaaag ccaggtccga ggccaaagtt 2220
ctccctgcca tccttggtgc cgtcctgccc cttcctcctt catgcctggg cctgcaggcc 2280
caccccagcc accactgagt ccactcggag tgccctgtgt tcctggagaa ggcattccag 2340
ggttgaatct tgtcccagcc tcagcctggg acacctaggt ggagagagtg gtctccgctc 2400
tgaattggat ccaggggacc tgggctcatt cttcttggct caccaaccct gcaggcctca 2460
tctttcccaa aacccacttt gtcttggtgg gagtgggtcc gcgctgctct gcagcagggg 2520
ctggggagtg gacagcatca ggtgggaaag tggagtccac cctcatgttt ctgtaggatt 2580
ctcaccgtgg ggctggaaga aaagagcatc gacttgattt ctccaaccac tcatccctct 2640
ttttctttct tccaccactc cccaccccag ctgtagttaa tttcagtgcc ttacaaatcc 2700
taagctcaga gaaagttcca tttccgttcc agagggaagg gaacctccct aggtccttcc 2760
ctggcttgtt ataacgcaaa gcttggttgt ttatgcaact ctatcttaag aactgcccag 2820
cctcagctga aaacccgaat ctgagaagga attgcgtcat gtaagggaag ctggaattaa 2880
gggagctgag ccagtcatgg ttgtggcgtg tgagtcagga gacctaggtt tcagcccctc 2940
tctactgtca gcgagctgtg caacgtgggc aagtcattgt cctctgagct gcagtttcct 3000
catctgtcac atcgctacag acaagacctc cctggaaccc ttctgattgt cttagacact 3060
gtggttgcaa aacccacgga aagcctcatt tgtgtggaaa gtcagaggaa aaatgatcca 3120
gtggacactt ggggattatc tgtcattcaa gatccttcct tcaaccccaa ggccagctcc 3180
catctcattt ccagaaaggc tcatacctgg cttgcaggga agcatctgtc ttgtcattcc 3240
aggtgccaga atcctctcag agtcattgaa gggtgttcac ccatcccacc caaggcttgg 3300
cacactgcca gtgtcttagc agggtcttgt gagggctggg ggcatccagg cactcagaag 3360
gcaaaggaac caccctaccc atttggcctc tggagggggc agaagaaaga aagaaacctc 3420
atcctatatt ttacaaagca tgtgaattct ggcattagct ctcataggag acccatgtgc 3480
ttccttgctc agtgcaaaac tgatgattct acttgctgta gatgaatggt taacacgagc 3540
tagttaaaca gtgccattgt tttgccagtg aagcctccaa ccctaagcca ctgggacggt 3600
ggccagagat gccagcagcc tctgtcgccc ttagtcatat aaccaaaatc cagaccttat 3660
ccacaacccg gggcttggaa aggaaggtat tttggaatca caccctccgg ttatgttgct 3720
ccagtaaaat cttgcctgga aagaggcagt cttcttagca tggtgagctg agttcatggc 3780
tttttttgt agccagtcct gtccctggcc atccatgtga tggttttgga tggagttaaa 3840
cttgatgcca gtgggcagtg catgtggaaa gtatcagagt aagcctctcc cctccagagc 3900
cctgagtttc ttggctgcat gaaggttttc tttagaatca gaattgtagc cagtttcttt 3960
ggccagaagg atgaatactt ggatattact gaaagggagg ggtggagatg ggtgtggcag 4020
tgtatggtgt gtgattttta ttttcttctt tggtcatggg ggccaaggag aaaggcatga 4080
atcttccctg tcaggctctt acagccacag gcactgtgtc tactgtctgg aagacatgtc 4140
cccgtggctg tggggccgct gcttctgttt aaataaaagt ggcctgg 4187

<210> 4
<211> 4186
<212> DNA
<213> Homo sapiens

<400> 4
ggcgcgaacc cgcagcgctt accgcgcggc gccgcaccat ggagcccgcc gtgtcgctgg 60
ccgtgtgcgc gctgctcttc ctgctgtggg tgcgcctgaa ggggctggag ttcgtgctca 120
tccaccagcg ctgggtgttc gtgtgcctct tcctcctgcc gctctcgctt atcttcgata 180
tctactacta cgtgcgcgcc tgggtggtgt tcaagctcag cagcgctccg cgcctgcacg 240
agcagcgcgt gcgggacatc cagaagcagg tgcgggaatg gaaggagcag ggtagcaaga 300
ccttcatgtg cacggggcgc cctggctggc tcactgtctc actacgtgtc gggaagtaca 360
agaagacaca caaaaacatc atgatcaacc tgatggacat tctggaagtg gacaccaaga 420
aacagattgt ccgtgtggag cccttggtga ccatgggcca ggtgactgcc ctgctgacct 480
ccattggctg gactctcccc gtgttgcctg agcttgatga cctcacagtg gggggcttga 540
tcatgggcac aggcatcgag tcatcatccc acaagtacgg cctgttccaa cacatctgca 600
ctgcttacga gctggtcctg gctgatggca gctttgtgcg atgcactccg tccgaaaact 660
cagacctgtt ctatgccgta ccctggtcct gtgggacgct gggtttcctg gtggccgctg 720
agatccgcat catccctgcc aagaagtacg tcaagctgcg tttcgagcca gtgcggggcc 780
tggaggctat ctgtgccaag ttcacccacg agtcccagcg gcaggagaac cacttcgtgg 840
aagggctgct ctactccctg gatgaggctg tcattatgac aggggtcatg acagatgagg 900
cagagcccag caagctgaat agcattggca attactacaa gccgtggttc tttaagcatg 960
tggagaacta tctgaagaca aaccgagagg gcctggagta cattcccttg agacactact 1020
accaccgcca cacgcgcagc atcttctggg agctccagga catcatcccc tttggcaaca 1080
accccatctt ccgctacctc tttggctgga tggtgcctcc caagatctcc ctcctgaagc 1140
tgacccaggg tgagaccctg cgcaagtgta cgagcagcac cacgtggtgc aggacatgct 1200
ggtgcccatg aagtgcctgc agcaggccct gcacaccttc caaaacgaca tccacgtcta 1260
ccccatctgg ctgtgtccgt tcatcctgcc cagccagcca ggcctagtgc accccaaagg 1320
aaatgaggca gagctctaca tcgacattgg agcatatggg gagccgcgtg tgaaacactt 1380
tgaagccagg tcctgcatga ggcagctgga gaagtttgtc cgcagcgtgc atggcttcca 1440
gatgctgtat gccgactgct acatgaaccg ggaggagttc tgggagatgt ttgatggctc 1500
cttgtaccac aagctgcgag agaagctggg ttgccaggac gccttccccg aggtgtacga 1560
caagatctgc aaggccgcca ggcactgagc tggagcccgc ctggagagac agacacgtgt 1620
gagtggtcag gcatcttccc ttcactcaag cttggctgct ttcctagatc cacactttca 1680
aagagaaacc cctccagaac tcccaccctg acagcccaac accaccttcc tcctggcttc 1740
caggggggcag cccagtggaa tggaaagaat gtgggatttg gagtcagaca agcctgagtc 1800
cagttccccg tttagaactc attagctgtg tgactctggg tgagtccctt aacccctctg 1860
agcccgggtc tcttcattag ttgaaaggga tagtaatacc tacttgcagg ttgttgtcat 1920
ctgagttgag cactggtcac attgaaggtg ctgggtaagt ggtagctctt gttgcttccc 1980
gttcagcgtc acatctgcag tggagcctga aaaggctcca cattaggtca cctgtgcaca 2040
gccatggctg gaatgatgaa ggggatacgc tggagttgcc ctgccatcgc ctccatcagc 2100
cagacgaggt cctcacagga gaaggacagc tcttccccac cctgggatct caggagggca 2160
gccacggagt ggggaggccc cagatgcgct gtgccaaagc caggtccgag gccaaagttc 2220
tccctgccat ccttggtgcc gtcctgcccc ttcctccttc atgcctgggc ctgcaggccc 2280
accccagcca ccactgagtc cactcggagt gccctgtgtt cctggagaag gcattccagg 2340
gttgaatctt gtcccagcct cagcctggga cacctaggtg gagagagtgg tctccgctct 2400
gaattggatc caggggacct gggctcattc ttcttggctc accaaccctg caggcctcat 2460
ctttcccaaa acccactttg tcttggtggg agtgggtccg cgctgctctg cagcaggggc 2520
tggggagtgg acagcatcag gtgggaaagt ggagtccacc ctcatgtttc tgtaggattc 2580
tcaccgtggg gctggaagaa aagagcatcg acttgatttc tccaaccact catccctctt 2640
tttctttctt ccaccactcc ccaccccagc tgtagttaat ttcagtgcct tacaaatcct 2700
aagctcagag aaagttccat ttccgttcca gagggaaggg aacctcccta ggtccttccc 2760
tggcttgtta taacgcaaag cttggttgtt tatgcaactc tatcttaaga actgcccagc 2820

ctcagctgaa aacccgaatc tgagaaggaa ttgcgtcatg taagggaagc tggaattaag 2880
ggagctgagc cagtcatggt tgtggcgtgt gagtcaggag acctaggttt cagcccctct 2940
ctactgtcag cgagctgtgc aacgtgggca agtcattgtc ctctgagctg cagtttcctc 3000
atctgtcaca tcgctacaga caagacctcc ctggaaccct tctgattgtc ttagacactg 3060
tggttgcaaa acccacggaa agcctcattt gtgtggaaag tcagaggaaa aatgatccag 3120
tggacacttg ggattatct gtcattcaag atccttcctt caaccccaag gccagctccc 3180
atctcatttc cagaaaggct catacctggc ttgcagggaa gcatctgtct tgtcattcca 3240
ggtgccagaa tcctctcaga gtcattgaag ggtgttcacc catcccaccc aaggcttggc 3300
acactgccag tgtcttagca gggtcttgtg agggctgggg gcatccaggc actcagaagg 3360
caaaggaacc accctaccca tttggcctct ggagggggca gaagaaagaa agaaacctca 3420
tcctatattt tacaaagcat gtgaattctg gcattagctc tcataggaga cccatgtgct 3480
tccttgctca gtgcaaaact gatgattcta cttgctgtag atgaatggtt aacacgagct 3540
agttaaacag tgccattgtt ttgccagtga agcctccaac cctaagccac tgggacggtg 3600
gccagagatg ccagcagcct ctgtcgccct tagtcatata accaaaatcc agaccttatc 3660
cacaacccgg ggcttggaaa ggaaggtatt ttggaatcac accctccggt tatgttgctc 3720
cagtaaaatc ttgcctggaa agaggcagtc ttcttagcat ggtgagctga gttcatggct 3780
tttttttgta gccagtcctg tccctggcca tccatgtgat ggttttggat ggagttaaac 3840
ttgatgccag tgggcagtgc atgtggaaag tatcagagta agcctctccc ctccagagcc 3900
ctgagtttct tggctgcatg aaggttttct ttagaatcag aattgtagcc agtttctttg 3960
gccagaagga tgaatacttg gatattactg aaagggaggg gtggagatgg gtgtggcagt 4020
gtatggtgtg tgatttttat tttcttcttt ggtcatgggg gccaaggaga aaggcatgaa 4080
tcttccctgt caggctctta cagccacagg cactgtgtct actgtctgga agacatgtcc 4140
ccgtggctgt ggggccgctg cttctgttta aataaaagtg gcctgg 4186

METHODS OF DIAGNOSING OR TREATING NEUROLOGICAL DISEASES AND CELL DEGENERATION

Cell death is a common feature occuring in two distinct forms in nature. Necrosis results from physical or chemical insult while apoptosis or programmed cell death results from a self-destruction program within the cell in response to internal and external stimuli. Latter process is a gene-directed form of cell death that is essential for normal development and maintenance of multicellular organisms. Recent work has clearly demonstrated that dysregulation of apoptosis may underlie the pathogenesis of a variety of diseases. Apoptosis has been reported to occur in conditions characterized by ischaemia, e.g. myocardial infarction and stroke. It has been implicated in a number of liver disorders including obstructive jaundice. Hepatic damage due to toxins and drugs is also associated with apoptosis in hepatocytes. Apoptosis has also been identified as a key phenomenon in some diseases of the kidney, i.e. polycistic kidney, as well as in disorders of the pancreas like alcohol-induced pancreatitis and diabetes. AIDS and neurodegenerative disorders like Alzheimer's and Parkinson's disease represent the most widely studied group of disorders where an excess of apoptosis has been implicated. Amyotrophic lateral sclerosis, retinitis pigmentosa, epilepsy and alcoholic brain damage are other neurological disorders in which apoptosis has been implicated.

Neurological diseases are widely spread within a population and have a strong impact not only on patients' life but also on society as such. Therefore, there is a strong need to elucidate the causes and the underlying pathogenesis of such neurological diseases. Among such neurological diseases, Alzheimer's disease (AD) has a predominant position. Alzheimer's disease, first described by the Bavarian psychiatrist Alois Alzheimer in 1907, is a progressive neurological disorder which begins with short term memory loss and proceeds to loss of cognitive functions, disorientation, impairment of judgement and reasoning and, ultimately, dementia. It is the most common cause of dementia. AD has been estimated to afflict 5 to 11 percent of the population over age 65 and as much as 47 percent of the population over age 85. Moreover, as adults, born during the population boom of the 1940's and 1950's, approach the age when AD becomes more prevalent, the control and treatment of AD will become an even more

significant health care problem. Familial forms of AD are genetically heterogeneous, but most with early onset are linked to mutations in the presenilin genes *PSEN1* and *PSEN2*, as well as to mutations of the amyloid precursor gene *APP*. The majority of AD patients have no obvious family history and are classified as sporadic AD. The neuropathology of AD is characterized by a substantial loss of neurons and synapses, and by the formation in brain of amyloid plaques and neurofibrillary tangles. Amyloid plaques are evenly distributed throughout the neocortex and the hippocampus, whereas neurodegeneration occurs predominantly in the inferior temporal lobes, the entorhinal cortex, and the hippocampus. Similar neurons in the frontal, parietal, and occipital lobes are largely preserved from degeneration even in severe end-stage AD. These observations indicate selective vulnerability of specific population of neurons. Factors that determine selective vulnerability of neurons in AD brains are unknown.

To elucidate the causes of cell degeneration and cell death is a general aim of the present invention. More specifically, the present invention aims at elucidating the causes and the underlying pathogenesis of neurological diseases, in particular Alzheimer's disease. It is therefore an object of the present invention to provide an insight into the pathogenesis of neurological diseases and to provide methods and materials which are suited for diagnosis and treatment of said diseases, cell degeneration and cell death.

The invention features an isolated nucleic acid molecule encoding a protein molecule whose amino acid sequence comprises the sequence shown in SEQ ID NO. 1 as well as the protein molecule according to SEQ ID NO.1. Hereinafter, the protein molecule of SEQ ID NO. 1 is denoted "SELADIN-1". One function of SELADIN-1 is to protect cells against degeneration and cell death. In particular, cells of the nerve system, muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, lung, trachea or placenta are protected against degeneration and/or cell death. Therefore, the present invention also features functional variants of SELADIN-1 which might have a modification of the given primary structure of SELADIN-1, but whose essential biological function remains unaffected. "Variants" of a protein molecule shown in SEQ ID NO.1 include for example proteins with conservative amino acid substitutions

in highly conservative regions. For example, isoleucine, valine and leucine can each be substituted for one another. Aspartate and glutamate can be substituted for each other. Glutamine and asparagine can be substituted for each other. Serine and threonine can be substituted for each other. Amino acid substitutions in less conservative regions include e.g.: Isoleucine, valine and leucine can each be substituted for one another. Aspartate and glutamate can be substituted for each other. Glutamine and asparagine can be subsituted for each other. Serine and threonine can be substituted for each other. Glycine and alanine can be substituted for each other. Alanine and valine can be substituted for each other. Methionine can be substituted for each of leucine, isoleucine or valine, and vice versa. Lysine and arginine can be substituted for each other. One of aspartate and glutamate can be substituted for one of arginine or lysine, and vice versa. Histidine can be substituted for arginine or lysine, and vice versa. Glutamine and glutamate can be substituted for each other. Asparagine and aspartate can be substituted for each other. Other examples of protein modifications include glycosilation and further posttranslational modifications. The invention also features the nucleic acid molecules encoding such functional variants of the protein molecule of SEQ ID NO. 1. Nucleic acid molecules can be DNA molecules, such as genomic DNA molecules or cDNA molecules, or RNA molecules, such as mRNA molecules. In particular, said nucleic acid molecule can be a cDNA molecule comprising a nucleotide sequence of SEQ ID NO. 2. The invention also features an isolated D N A molecule capable of hybridizing with the complement of the cD N A described in SEQ ID NO. 2 under stringent conditions. Examples for stringent conditions include (i) 0.2xSSC (standard saline citrate) and 0.1 % SDS at 60 °C and (ii) 50 % formamide, 4xSSC, 50 mM HEPES, pH 7.0, 10x Denhardt's solution, 100 µg/ml thermally denatured salmon sperm DNA at 42 °C.

In another aspect, the invention features a vector comprising a nucleic acid encoding a protein molecule shown in SEQ ID NO. 1. It also features a vector comprising a nucleic acid molecule encoding a protein molecule, the function of which is to protect cells against degeneration and/or cell death, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO. 1 or a functional variant thereof. In preferred embodiments, a virus, a bacteriophage, or a plasmid comprises the

described nucleic acid. In particular, a plasmid adapted for expression in a bacterial cell comprises said nucleic acid molecule, e.g. a nucleic acid molecule encoding a protein molecule shown in SEQ ID NO. 1, and the regulatory elements necessary for expression of said molecule in the bacterial cell. In a further aspect, the invention features a plasmid adapted for expression in a yeast cell which comprises said nucleic acid molecule, e.g. a nucleic acid molecule encoding a protein molecule shown in SEQ ID NO. 1, and the regulatory elements necessary for expression of said molecule in the yeast cell. In another aspect, the invention features a plasmid adapted for expression in a mammalian cell which comprises a nucleic acid molecule, e.g. a nucleic acid molecule encoding a protein molecule shown in SEQ ID NO.1, and the regulatory elements necessary for expression of said molecule in the mammalian cell.

In a further aspect, the invention features a cell comprising a nucleic acid molecule encoding a protein molecule shown in SEQ ID NO. 1. The invention also features cells comprising a nucleic acid molecule encoding a protein molecule whose function is to protect cells against degeneration and/or cell death and whose amino acid sequence comprises the sequence shown in SEQ ID NO. 1 or a functional variant thereof. It also features cells comprising a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions. In preferred embodiments, said cell is a bacterial cell, a yeast cell, a mammalian cell, or a cell of an insect. In particular, the invention features a bacterial cell comprising a plasmid adapted for expression in a bacterial cell, said plasmid comprising a nucleic acid molecule which encodes a protein molecule shown in SEQ ID NO. 1, and the regulatory elements necessary for expression of said molecule in the bacterial cell. The invention also features a yeast cell comprising a plasmid adapted for expression in a yeast cell, said plasmid comprises a nucleic acid molecule encoding a protein molecule shown in SEQ ID NO. 1, and the regulatory elements necessary for expression of said molecule in the yeast cell. It further features a mammalian cell comprising a plasmid adapted for expression in a mammalian cell, said plasmid comprising a nucleic acid molecule which encodes a protein molecule shown in SEQ ID NO.1, and the regulatory elements necessary for expression of said molecule in the mammalian cell.

The invention further features an antibody specifically immunoreactive with an immunogen, wherein said immunogen is shown in SEQ ID NO. 1 or wherein said immunogen is a protein molecule, the function of which is to protect cells against degeneration and/or cell death, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO. 1 or a functional variant thereof. In another aspect, the invention aims at a method of detecting pathological cells in a subject which comprises immunocytochemically staining cells with the aforementioned antibody, wherein a low degree of staining in said cell compared to a reference cell representing a known health status indicates a pathological change of said cell. The invention is particularly suited to detect pathological structures in the brain of a subject – the detection method comprises immunocytochemically staining said pathological structures with said antibody. It is also especially suited to detect pathological cells of the muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, lung, trachea or placenta.

In another aspect, the invention features a method of diagnosing or prognosing a disease, in particular a neurological disease, in a subject comprising:
determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

and comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby diagnosing or prognosing a disease, in particular a neurological disease, in said subject.

In another aspect, the invention features a method of monitoring the progression of a disease, in particular a neurological disease, in a subject, comprising:

determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

and comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby monitoring progression of a disease, in particular a neurological disease, in said subject.

In still a further aspect, the invention features a method of evaluating a treatment for a disease, in particular a neurological disease, in a subject, said method comprising:

determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

and comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby evaluating a treatment for a disease, in particular a neurological disease, in said subject.

In a further aspect, the invention features a kit for diagnosis, or prognosis of a disease, said kit comprising:

(1) at least one reagent which is selected from the group consisting of reagents that selectively detect

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

(2) instructions for diagnosing, or prognosing said disease by

(i) detecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) in a sample from said subject;

and

(ii) diagnosing, or prognosing said disease, wherein

a varied level, or activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) compared to a reference value representing a known health status;

or a level, or activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) similar or equal to a reference value representing a known disease status indicates diagnosis, or prognosis of said disease.

In a further aspect, the kit may be used in monitoring success or failure of a therapeutic treatment of said subject. It can also be used in monitoring the progression of a disease.

Preferred embodiments of the above mentioned methods and kit of diagnosing or prognosing diseases, or monitoring the progression thereof, or evaluating a treatment thereof, are now disclosed in detail.

In a preferred embodiment, the function of said protein molecule or a functional variant thereof is to protect cells from degeneration and/or cell death.

In another preferred embodiment, said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein molecule, the function of which is to protect cells against cell degeneration and/or cell death.

In preferred embodiments, said subjects suffer from Alzheimer's disease and related neurofibrillary disorders, or degenerative states, e.g. neurodegenerative states, characterized by cell degeneration or cell death. Further examples of neurological diseases are Parkinson´s disease, Huntington disease, amyotrophic lateralsclerosis and Pick´s disease.

It is particularly preferred that said sample is a brain tissue or other body cells including cells of the muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, lung, trachea, or placenta. The sample might also be cerebrospinal fluid or another body fluid.

According to the present invention, a reduction in the level, or activity, or both said level and said activity, of (i) a transcription product of a D N A molecule encoding a protein molecule, whose amino acid sequence comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof or (ii) a protein molecule whose amino acid sequence comprises the sequence shown in SEQ ID NO. 1 or a functional variant thereof, in a sample from said subject relative to a reference value representing a known health status indicates the presence of a pathological status in said subject. In particular, a reduction in the level, or activity, or both said level and said activity of SELADIN-1 or *SELADIN-1* transcripts in said subject's brain regions affected heavily by neurodegeneration relative to a reference value representing a known health status indicates a diagnosis or prognosis of Alzheimer's disease. Predominantly neurons within the inferior temporal lobe, the entorhinal cortex, the hippocampus and the amygdala degenerate in Alzheimer's disease.

It might be preferred that said subject has previously been determined to have one or more factors indicating that such subject is afflicted with a disease under study, in particular a neurological disease.

In preferred embodiments, said subject can be a human, an experimental animal, e.g. a rat or a mouse, a domestic animal, or a non-human primate, e.g. a monkey. The experimental animal can be an animal model for a disorder, e.g. a transgenic mouse with an Alzheimer's-type neuropathology.

In preferred embodiments, at least one of said substances is detected using an immunoassay, an enzyme activity assay and/or a binding assay.

In preferred embodiments, measurement of the level of transcription products of the *SELADIN-1* gene, or a functional variant thereof, is performed in body cells using Northern blots with probes specific for the *SELADIN-1* gene or said variant. Quantitative PCR with primer combinations to amplify *SELADIN-1* gene-specific sequences from cDNA obtained by reverse transcription of RNA extracted from body cells of a subject can also be applied. These techniques are known to those of ordinary skill in the art (see e.g. Watson et al., Rekombinierte DNA, 2nd edition, Spektrum Akademischer Verlag GmbH, Heidelberg, 1993; Watson et al., Recombinant DNA, 2nd ed. W.H. Freeman and Company, 1992).

In preferred embodiments, said level or activity of the protein molecule shown in SEQ ID NO. 1, or a functional variant or fragment thereof, is detected using an immunoassay. These assays can measure the amount of binding between said protein molecule and an anti-protein antibody, e.g. an anti-SELADIN-1 antibody, by the use of enzymatic, chromodynamic, radioactive, or luminescent labels which are attached to either the anti-protein antibody or a secondary antibody which binds the anti-protein antibody. In addition, other high affinity ligands may be used. Immunoassays which can be used include e.g. ELISAs, Western blots and other techniques known to those of ordinary skill

in the art (see Harlow et al., Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

The antibody or ligand to be used should preferably specifically detect SELADIN-1 or a functional variant or fragment thereof. It is preferred that it does not substantially interact with any other protein present in said sample.

Monoclonal antibodies capable of recognizing a protein molecule of SEQ ID NO. 1 or a functional variant or fragment thereof can be prepared using methods known in the art (see e.g. Köhler and Milstein, Nature 256, 495 - 497 1975; Kozbor et al., Immunol. Today 4, 72, 1983; Cole et al., Monoclonal antibodies and cancer therapy, Alan R. Liss, Inc., pp 77 - 96, 1985; Marks et al., J. Biol. Chem., 16007 - 16010, 1992; the contents of which are incorporated herein by reference). Such monoclonal antibodies or fragments thereof can also be produced by alternative methods known to those of skill in the art of recombinant DNA technology (see e.g. Sastry et al, PNAS 86: 5728, 1989; ; Watson et al., Rekombinierte DNA, 2nd ed., Spektrum Akademischer Verlag GmbH, 1993; Watson et al, Recombinant DNA, 2nd ed., W. H. Freeman and Company, 1992; the contents of which are incorporated herein by reference). Monoclonal antibodies useful in the methods of the invention are directed to an epitope of SELADIN-1 or a functional variant or fragment thereof, such that the complex formed between the antibody and SELADIN-1, or between the antibody and said functional variant or fragment, can be recognized in detection assays. The term "antibodies" encompasses all forms of antibodies known in the art, such as polyclonal, monoclonal, chimeric, recombinatorial, single chain antibodies as well as fragments thereof which specifically bind to SELADIN-1, or to a functional variant or fragment thereof.

Antibodies or ligands might also be used in detecting specifically molecules mentioned in the above described methods and kit under g) and h) above.

If luminescent labels are used in any detection assay, it is preferred to use a confocal optical set-up.

In further preferred embodiments, said reference value is that of a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) described above in a sample from a subject not suffering of the disease under study, in particular a neurological disease such as Alzheimer's disease. The healthy subject can be of the same weight, age, and gender as the subject who is being diagnosed or prognosed for said disease. In some cases, it might be preferred to use a reference value from the subject which is diagnosed.

In a preferred embodiment, the level, or the activity, or both said level and said activity, of at least one of said substances (a) to (h) described above in a sample is determined at least twice, e.g. at two points which are weeks or months apart. The levels or activities at these two time points are compared in order to monitor the progression of said disease. It might be preferred to take a series of samples over a period of time. In further preferred embodiments, said subject receives a treatment prior to one or more of said sample gatherings.

In another aspect, the invention features a method of treating or preventing a disease, in particular a neurological disease, in a subject comprising administering to said subject in a therapeutically effective amount an agent or agents which affect a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f).

In a preferred embodiment, the function of said protein molecule or a functional variant thereof is to protect cells from degeneration and/or cell death.

In another preferred embodiment, said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein molecule, the function of which is to protect cells against cell degeneration and/or cell death.

In preferred embodiments, said subjects suffer from Alzheimer's disease and related neurofibrillary disorders, or degenerative states, such as neurodegenerative states, characterized by cell degeneration or cell death. Further examples of neurological diseases are Parkinson´s disease, Huntington disease, amyotrophic lateralsclerosis and Pick´s disease.

In preferred embodiments, the method comprises the application of per se known methods of gene therapy nucleic acid technology to administer said agent or said agents.

In general, gene therapy includes several approaches: molecular replacement of a mutated gene, addition of a new gene resulting in the synthesis of a therapeutic protein,

and modulation of endogeneous cellular gene expression by recombinant expression methods or by drugs. Gene-transfer techniques are described in detail (see e.g. Behr, Acc. Chem. Res. 26, 274 - 278, 1993; Mulligan, Science 260, 926 - 931, 1993; the contents of which are incorporated herein by reference) and include direct gene-transfer techniques such as mechanical microinjection of DNA into a cell as well as indirect techniques employing biological vectors (like recombinant viruses, especially retroviruses) or model liposomes, or techniques based on transfection with DNA coprecipitation with polycations, cell membrane perturbation by chemical (solvents, detergents, polymers, enzymes) or physical means (mechanic, osmotic, thermic, electric shocks). The postnatal gene transfer into the central nervous system has been described in detail (see e.g. Wolff, Current Opinion in Neurobiology, 3, 743 - 748, 1993; the contents of which are incorporated herein by reference).

In preferred embodiments, the method comprises grafting donor cells into the central nervous system, preferably the brain, of said subject, said subject or donor cells preferably treated so as to minimize or reduce graft rejection, wherein said donor cells are genetically modified by insertion of at least one transgene encoding said agent or agents. Said transgene might be carried by a viral vector, in particular a retroviral vector. The transgene can be inserted into the donor cells by a nonviral physical transfection of DNA encoding a transgene, in particular by microinjection. Insertion of the transgene can also be performed by electroporation, chemically mediated transfection, in particular calcium phospate transfection, liposomal mediated transfection, etc.

In preferred embodiments, said agent is a therapeutic protein which can be administered to said subject, preferably a human, by a process comprising introducing subject cells into said subject, said subject cells having been treated *in vitro* to insert a DNA segment encoding said therapeutic protein, said subject cells expressing *in vivo* in said subject a therapeutically effective amount of said therapeutic protein. Said DNA segment can be inserted into said cells *in vitro* by a viral vector, in particular a retroviral vector.

In preferred embodiments, the therapeutic nucleic acid or protein reduces or prevents the degeneration of cells, in particular neurons and slows brain amyloid formation.

In another aspect, the invention features an agent which affects an activity, or level, or both said activity or level, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f).

Preferably, the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death. Preferably, said D N A molecule capable of

hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein, whose function is to protect cells from degeneration and/or cell death.

In another aspect, the invention features a medicament comprising such an agent.

In still another aspect, the invention features an agent for treating or preventing a disease, in particular a neurological disease, which agent affects an activity, or level, or both said activity or level, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f).

In preferred embodiments, said diseases are degenerative states characterized by cell degeneration or cell death or Alzheimer's disease and related neurofibrillary disorders. Further examples of neurological diseases are Parkinson's disease, Huntington disease, Amyotrophic lateralsclerosis, Pick's disease.

Preferably, the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death. Preferably, said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein, whose function is to protect cells from degeneration and/or cell death.

In a further aspect, the invention features the use of an agent, for preparation of a medicament for treating or preventing a neurological disease, which agent affects an activity, or level, or both said activity or level, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(h) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f).

Preferably, the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death. Preferably, said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO.2 encodes a protein molecule, whose function is to protect cells against degeneration and/or cell death.

In preferred embodiments, said diseases are Alzheimer's disease and related neurofibrillary disorders, or degenerative states, in particular neurodegenerative states, characterized by cell degeneration or cell death. Further examples of neurological diseases are Parkinson's disease, Huntington disease, Amyotrophic lateralsclerosis, Pick's disease.

In a further aspect, the invention features a method for identifying an agent that affects an activity, or level, or both said activity or level, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

comprising the steps of:

(i) providing a sample containing at least one substance which is selected from the group consisting of (a) to (f),

(ii) contacting said sample with at least one agent,

(iii) comparing an activity, or level, or both said activity and level, of at least one of said substances before and after contacting.

Preferably, the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death. Preferably, said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein molecule, whose function is to protect cells against degeneration and/or cell death.

Other features and advantages of the invention will be apparent from the following detailed description of the figures, the examples and the claims.

Figure 1 depicts the selective vulnerability of brain regions in Alzheimer's disease. Predominantly neurons within the inferior temporal lobe, the entorhinal cortex, the

hippocampus and the amygdala degenerate in Alzheimer´s disease (Terry et al., Annals of Neurology, 10, 184-192, 1981). These brain regions are predominantly involved in the processing of learning and memory functions. In contrast, neurons within the frontal cortex, the occipital cortex and the cerebellum are largely intact and preserved from the neurodegenerative process in Alzheimer´s disease.

Figure 2 discloses the identification of genes differentially expressed in brain regions from Alzheimer´s disease patients. Brain areas with massive neuronal cell loss as well as areas with largely preserved neurons were identified and RNA extracted. Synthesis of cDNA was performed using an oligo-dT primer followed by PCR using the oligo-dT primer in combination with random primers and (α^{35}S)-dATP. Reactions were separated on DNA sequencing gels, DNA bands visualized by autoradiography and bands lighting up in different intensities were cut out. DNA fragments were reamplified by PCR, cloned in *E. coli* and sequences determined. Expression and functional analyses were performed.

Figure 3 depicts the specifications of Alzheimer´s disease brain tissue as it was used in the examples. Brain tissues from Alzheimer´s disease patients and control subjects were removed within 6 hours of death, and immediately frozen on dry ice. For RNA extraction tissue sections from the inferior temporal lobe and frontal cortex were chosen.

Figure 4 discloses the quantification of *SELADIN-1* transcripts in brain tissue from Alzheimer´s disease and control subjects by Northern blot analyses. Transcript levels were significantly lower in brain regions with severe neurodegeneration, i. e. temporal lobe in Alzheimer´s disease (AD1-3) but not in normal brain (NB1-3), as compared to protected brain regions, i. e. frontal lobe. This decrease was specific as indicated by unchanged ß-actin transcript levels used to control for equal loading of RNA.

Figure 5 depicts the transcription levels of the *SELADIN-1* gene in different human brain regions. The *SELADIN-1* gene was found to be expressed throughout the human brain. In particular transcription levels are high in all cortical areas, the hippocampus, the

amygdala, the spinal cord, and the medulla. Note the unchanged levels in temporal lobe versus frontal lobe in this brain derived from a cognitively normal control subject without any signs of Alzheimer´s disease. The analysis of ß-actin transcripts was used as loading control.

Figure 6 depicts the distribution of *SELADIN-1* transcripts in human tissues. Comparable samples of RNA were spotted on nitrocellulose filters and *SELADIN-1* transcripts were quantified by hybridization using a labeled SELADIN-1 gene specific probe. Significant levels of *SELADIN-1* gene transcripts were found in all brain regions tested. Transcripts were also detected in other tissues, however, strong variations in signal intensity indicated a tissue specific regulation of *SELADIN-1* expression.

Figure 7 depicts the expression of the *SELADIN-1* gene in rat brain cortex, hippocampus and basal nucleus analyzed by in situ hybridization. This staining pattern along with the higher magnifications indicate that *SELADIN-1* is predominantly expressed in neurons. No significant hybridization signals were observed with glial cells.

Figure 8 depicts the expression of *SELADIN-1* in rat brain nuclei. Strong *SELADIN-1* expression was found in the occulomotor, paraventricular, red and facial nuclei. Higer magnifications indicate predominant hybridization with neurons. No significant hybridization signals were observed with glial cells.

Figure 9 depicts the expression of *SELADIN-1* in rat brain hippocampus and substantia nigra. In situ hybridization with *SELADIN-1* transcripts was detected by photoemulsionautoradiography, confirming the neuron specific expression of this gene.

Figure 10 discloses the subcellular localization of a SELADIN-1-EGFP (enhanced green fluorescent protein) fusion in transfected cos cells. The confocal micrographs show the co-localization of the SELADIN-1-EGFP fusion with the golgi specific stain BODIPY TR ceramide indicating localization of SELADIN-1 in the Golgi apparatus and the endoplasmic reticulum.

Figure 11 discloses that the SELADIN-1-EGFP fusion does not localize to mitochondria in transfected cos cells in spite of a putative mitochondrial targeting sequence close to the N-terminus of the SELADIN-1 protein. The confocal micrographs show the different staining patterns caused by the SELADIN-1-EGFP fusion and the specific mitochondrial stain Mito Tracker Red CM-H_2XRos.

Figure 12 discloses structural features of the SELADIN-1 protein based on multiple sequence alignments and secondary structure predictions. Near the N-terminus the SELADIN-1 protein contains a putative mitochondrial localization signal that appears to be inactive in transfected cos cells or when used in EGFP fusions. The central region of the protein contains a sequence that is homologous to a family of oxidoreductases and that contains a FAD site for covalent binding. The protein is predicted to contain five transmembrane regions. The expression in neurons, the co-localization in the Golgi apparatus and the endoplasmic reticulum of the SELADIN-1 protein, the amyloid precursor protein (APP) and the presenilins PS1 and PS2 and furthermore the transmembrane character suggest a functional relationship between these proteins. Mutations in both APP and presenilins were shown to cause an increase in the production of ß-amyloid. In a similar way the SELADIN-1 protein might be involved in common biological pathways influencing the processing of the amyloid precursor protein and the generation of Aß. Using the SELADIN-1 protein as a probe, interaction partners can be identified which might represent new AD drug targets.

Figure 13 discloses the protein sequence of SELADIN-1 (SEQ ID NO. 1). The full length protein consists of 516 amino acid residues. The sequence is given in the one letter amino acid code.

Figure 14 discloses the nucleotide sequence of the cloned *SELADIN-1* cDNA (SEQ ID NO. 2) comprising 4248 nucleotides. The coding sequence for the SELADIN-1 protein starts at nucleotide position 100 and stops at position 1648.

Figure 15 discloses the comparison of nucleotide sequences of the cloned *SELADIN-1* cDNA comprising 4248 nucleotides and the KIAA0018 cDNA comprising 4186

nucleotides. A significant difference exists at position 1228 of the *SELADIN-1* sequence where a C nucleotide (C/G basepair) is missing in the *KIAA0018* sequence. This results in a frameshift in the open reading frame in the *KIAA0018* sequence relative to the *SELADIN-1* sequence. The consequence is that the translation product of the *KIAA0018* gene is 390 amino acids in length compared to 516 amino acid residues of the SELADIN-1 translation product. In addition to the difference in length, the frameshift causes a difference between the C-terminal 14 amino acids of the KIAA0018 protein and the corresponding sequence area of the SELADIN-1 polypeptide (pos. 377 - 390). The coding sequence for the SELADIN-1 protein starts at nucleotide position 100 and stops at position 1648.

Figure 16 shows the amino acid sequence of SELADIN-1. A differential display approach (von der Kammer, H. et al., Nucleic acid research, 27, 2211, 1999; von der Kammer, H. et al., J. Biol. Chem. 273, 14538, 1998) to identify genes that are differentially expressed in selectively vulnerable cell populations in the inferior temproal cortex with confirmed neurodegeneration and in the largely unaffected frontal or sensory-motor cortex of the same subject in three brains with a histopathological diagnosis of Alzheimer's disease and post mortem time intervlas of less than four hours. By using forty different primer combinations, twenty-eight of thirty-six differentially expressed cDNAs were cloned and sequenced. These cDNAs were further analyzed by reverse Northern blotting (Poirier G.M.-C. et al., Nucleic Acid Res., 25, 913, 1997; Van Gelder R. N. et al., Proc. Natl. Acad. Sci. USA, 87, 1663, 1990) to confirm differential expression between the two AD brain regions. Expression of one of these cDNAs was markedly lower in the inferior temporal lobe than in the sensory-motor cortex. Therefore, the potential importance of this transcript for the selective vulnerability in AD brain has been investigated. The cDNA sequence consisted of 4248 nucleotides and encoded an open reading frame of 516 amino acid residues. Due to a cytidine insertion at nucleotide position 1167, this sequence differed from the much shorter coding region of its homolog KIAA0018 deposited in GenBank (Nomura et al., D N A Res. 1, 27, 1994; GenBank database accession HUMRSC390D13643,1, 1992; DIMH Human Q15392, 1998). The new gene has been designated *SELADIN-1*. The homology domain to oxido-reductases are highlighted in red; the homologies to "diminuto like proteins" of

other species are underlined. The first 21 amino acid residues represent a putative signal peptide. One possible caspase recognition motif is highlighted in yellow. This putative caspase recognition motif "LEVD" is present within the SELADIN-1 amino acid sequence at position 121 – 125. *In vitro* cleavage of SELADIN-1 by caspase 3 or 6 generated four different SELADIN-1 fragments of approximately 50, 40, 30 and 20 kDa, respectively. Secondary structure predictions revealed at least four possible transmembrane domains.

Figure 17 shows Northern blots of Alzheimer's disease (AD) brain and normal control brain. In AD brains, the expression of *SELADIN-1* was substantially lower in the inferior temporal lobe compared to the frontal cortex. In contrast, there was no difference in expression between these two regions in normal control brains (Fig. 17 A, B). Thus, the differential expression of *SELADIN-1* between temporal and frontal cortex within individual AD brains initially observed by both differential display and reverse Northerns, was independently confirmed in three other patients. *SELADIN-1* is strongly expressed throughout the normal human brain with highest expression in the cortices, in the medulla oblongata and the spinal cord as well as in substantia nigra and the hippocampus (Fig. 17B). **A** 10 µg of total RNA per lane, extracted with Trizol Reagent (Gibco) from the frontal cortex or the inferior temporal cortex of three different AD brains were separated on a 0.8 % formaldehyde-agarose gel and blotted on a Hybond-N+-Nylon Membrane (Amersham). Brain 1: post mortem time interval 3:30 hours, male, 72 years. Brain 2: post mortem time interval 1:30 hours, male, 62 years. Brain 3: post mortem time interval 4 hours, female, 63 years. Control brain: normal brain, post mortem time interval 1:10 hours, female, 80 years. The blots were hybridized with a ^{32}P-labeled c D N A probe of *Seladin-1* from nucleotide 1 – 3505 and with a ^{32}P-labeled c D N A control probe of human β-actin as provided by Clontech for the human brain multiple tissue northern blot II and III. **B** Human brain multiple tissue Northern blot II (Clontech 7755-1) and III (Clontech 7750-1) containing 2 µg of polyA+ RNA per lane from 16 different human brain regions. Blots were hybridized with the same probes as described in A.

Figure 18 shows the expression of *Seladin-1* in rat brain. *In situ* hybridization on paraformaldehyde fixed cryostat sections was performed as described by Hartman et al. (Developmental Neuroscience 17, 246, 1995). A 650 bp and a 900 bp fragment of the open reading frame of *Seladin-1* were PCR amplified using the following primer pairs:
1s (76-99) 5' GCG CTT ACC GCG CGG CGC CGC ACC 3' (SEQ ID NO. 3)
1as (749-726) 5' GAC CAG GGT ACG GCA TAG AAC AGG 3' (SEQ ID NO. 4)
3s (803-826) 5' AGA AGT ACG TCA AGC TGC GTT TCG 3' (SEQ ID NO. 5) and
3as (1749-1726) 5' TTC TCT TTG AAA GTG TGG ATC TAG 3' (SEQ ID NO. 6).
PCR fragments were cloned in pGEM-Teasy vector (Promega), cut with EcoRI and cloned in pBluescript KS+. The orientation of the EcoRI cloned fragments was analyzed by PCR. Using the Ambion Maxiscript kit, ^{35}S-UTP labeled antisense and sense riboprobes were generated on NotI and ClaI linearized plasmids with T3 and T7-Polymerase, respectively, according to the manufacturers instructions. Hybridized sections were dipped in NTB-3 photographic emulsion (Kodak), exposed for 5 weeks and counterstained in Mayer's hemalum. **A, D, G** show photomicrographs of the emulsion dipped sections. **pvn** paraventricular nucleus, **bnM** basal nucleus of Meynert, **amy** amygdala, **ocmn** oculomotor nucleus, **rn** red nucleus, **fn** facial nucleus. **B** is a darkfield illumination blow up of the hippocampal region. **dg** dentate gyrus. **C** is a darkfield illumination blow up of the cortical layer five **cl V. E, H** show brightfield higher magnification photomicrographes of the regions of interest from D and G. **F, I** DIC (differential interference contrast) illuminations in higher magnification of E and H to demonstrate single neurons stained with silver grains. In rat brain, expression of *SELADIN-1* was high in the hippocampal region CA3 (Fig. 18 A, B), in the pyramidal neurons of cortical layer five (Fig. 18 A, C), in the amygdala (Fig. 18 A), in the magnocellular neurons of the basal nucleus of Meynert (Fig. 18 A) and in the reticular zone of the substantia nigra (data not shown). In addition, transcripts were also detected in several brain nuclei including the paraventricular nucleus (Fig. 18 A), the oculomotor nucleus (Fig. 18 D, E), the facial nucleus (Fig. 18 G, F) as well as the red nucleus (Fig. 18 D, E).

Figure 19 shows *in situ* hybridization of human AD (**A-D**) and normal brain (**E-H**). *In situ* hybridization on embedded sections was performed as described (U. Süsens, Dev. Neurosci. 19, 410, 1997). The ^{35}S-UTP labeled riboprobe was derived from the first 650 nucleotides of the open reading frame of *Seladin-1* cloned in pBluescript KS+ as described in Figure 18. The hybridized slides were dipped in Kodak NTB-2 emulsion, exposed for 4 weeks. After development, sections were stained with Giemsa. **A, C, E and G** show darkfield illuminations and **B, D, F, H** the corresponding brightfield photomicrographes. To enhance the visibility of the silver grains in the brightfield picture higher magnification is shown. **A, B** representative hybridization pattern of *Seladin-1* in midfrontal cortex of AD brain. **C, D** representative hybridization pattern of *Seladin-1* in superior temporal cortex of AD brain. **E, F** representative hybridization pattern of *Seladin-1* in midfrontal cortex of normal brain. **G, H** representative hybridization pattern of *Seladin-1* in superior temporal cortex of normal brain. Arrowheads indicate neurons packed with silver grains; arrows indicate the neurons with only few grains (D). *In situ* hybridization of human AD and control brains to study the expression of *SELADIN-1* within single neurons, demonstrated that *SELADIN-1* mRNA was reduced in the remaining neurons of the temporal cortex in comparison to the neurons in the frontal cortex in the AD brains (Fig. 19, A-D, arrows). In contrast, in normal brains, neuronal expression of *SELADIN-1* was identical between the frontal cortex and the temporal cortex (Fig. 19, E-H, arrowheads), confirming the data from differential display and Northern blot analyses. Reduced levels of *SELADIN-1* mRNA in the temporal cortex in comparison to the frontal cortex in the AD brain were not only due to cell loss but were also reduced within the remaining neurons.

Figure 20. To analyze SELADIN-1 function as a putative oxido-reductase, human H4 neuroglioma cells were stably transfected with Seladin-1 fused at its C-terminus to EGFP (enhanced green fluorescence protein, Clontech). **A** 10 and 16 hours after incubation of three seladin-1-EGFP clones and three EGFP-control clones in OptiMEM1 containing 200 µM H_2O_2, cells remaining attached to the culture dish as well as cells in the supernatant were harvested and stained with 7-Amino-actinomycin D (7-ADD) as a standard flow cytometric viability probe to distinguish viable from non viable cells. Only

membranes of dead and damaged cells are permeable to this D N A dye and stain positive. Live/dead counts were done on FACSCalibur (Becton Dickinson) counting 10^5 cells per clone. Means of 2 experiments in triplicate are shown (± SEM). All SELADIN-1 expressing clones tolerated H_2O_2-induced oxidative stress much better than either non-transfected or EGFP expressing clones. After ten hours treatment with 200 µM H_2O_2 nearly 90 % of the SELADIN-1 expressing cells and 75 – 80 % of the control cells were viable; sixteen hours after incubation with 200 µM H_2O_2, however, 80 % of the SELADIN-1 expressing cells were still alive whereas only 52 % of the control cells were alive at this time point. Untreated control clones revealed a maximum of 5 % dead cells at equivalent time intervals. Increased survival rates in SELADIN-1 expressing cells after prolonged exposure to oxidative stress was confirmed by two independent approaches: First, live/dead counts were done on trypan blue stained cells on cell culture dishes and visualized in phase-contrast microscopy in ten randomly chosen fields. Second, nuclei of cells grown on coverslips and fixed with 4 % paraformaldehyde were stained with Hoechst dye 33342 (Molecular Probes) and visualized by fluorescence microscopy (data not shown). These measures confirmed that expression of SELADIN-1 conferred resistance against induction of cell death.

B To determine an early marker for apoptotic cell death, the activity of caspase 3 in cell lysates of three SELADIN-1-EGFP clones and three EGFP-control clones was measured using the caspase 3 assay kit from Pharmingen. After induction of apoptosis with 200 µM H_2O_2 for 2 or 4 hours, respectively, cells were washed briefly in PBS and lysed in 10 mM Tris-HCl, pH 7.5, 10 mM NaH_2PO_4, pH 7.5, 130 mM NaCl, 1 % Triton-X-100, 10 nM NaPPi (2 million cells/ml). 50 µl of the cell lysates were incubated in 200 µl HEPES buffer for 1 hour at 37 °C with 5 µg of the caspase 3 fluorogenic substrate Ac-DEBD-CHO in a 96 multiwell plate. The AMC liberated from Ac-DEVD after caspase cleavage was measured on a spectrofluorometer (Spectramax Gemini, Molecular Devices) with an excitation wavelength of 380 nm and an emission wavelength spectrum from 420 – 460 nm. Means of caspase 3 activity, measured in RFU (relative fluorescence units) of two experiments in triplicates are shown (± SEM). Two hours after induction of apoptosis with 200 µM H_2O_2, caspase 3 activity was not detectable in either SELADIN-1-EGFP clones or in the EGFP-control clones. After 4 hours, however, the activity of caspase 3 strongly increased and was found to be approximately two-fold

higher in three EGFP-control clones as compared to three SELADIN-1-EGFP clones. This increase in caspase 3 activity was blocked in either condition by the caspase inhibitor Ac-DEVD-CHO.

Figure 21 shows the subcellular localization of SELADIN-1. 114 human neuroglioma cells that stable express a fusionprotein of SELADIN-1 with the N-terminus of EGFP (Clontech) were grown on coverslips and fixed in 4 % paraformaldehyde in PBS or treated for 45 minutes with 250 nM of the red fluorescent mitochondrial stain MitoTracker red CM H_2Xros (Molecular Probes) before fixation. After fixation cells that have not been prestained with the MitoTracker were permeabilized in 0.2 % Triton-X 100 in PBS and blocked over night at 4 °C in 5 % low fat milk, 0.1 % Triton-X 100 in PBS. Cells were incubated for 2 hours at room temperature with an monoclonal antibody against the mouse anti-protein disulfide isomerase (antiPDImAb, StressGen Biotechnologies Corp.), a marker for the endoplasmic reticulum, washed and incubated for another hour with an anti-mouse IgG, CY3 labeled secondary antibody (Amersham). Cells were visualized with confocal laser scanning microscopy. **A, D** Subcellular distribution of the green fluorescent SELADIN-1-EGFP fusionprotein. **B** Staining of the endoplasmatic reticulum with the antiPDImAb and the red fluorescent CY3 labeled secondary antibody. **C** Overlay from A and B shows the colocalization of SELADIN-1 with the ER-marker, indicated as yellow fluorescence. **E** Staining of the mitochondria with the red fluorescence MitoTracker CM H_2Xros. **F** Overlay of D and E. These colocalization studies with markers and antibodies against several subcellular organelles indicated that SELADIN-1-EGFP mainly localized to the endoplasmatic reticulum and not to the mitochondria, despote the presence of a putative mitochondrial localization signal at the N-terminus of SELADIN-1.

Taken together a novel gene *SELADIN-1* that has homologies to FAD-dependent oxido-reductases has been identified. It has been shown that it was down-regulated in selectively vulnerable regions of AD brain. *In situ* hybridization of AD brain sections demonstrated that the reduced mRNA levels are not only due to neuronal loss in affected areas but also reflects reduced mRNA expression of the remaining neurons. Expression of *SELADIN-1* in H4 cells conferred resistance to apoptosis by oxidative

stress, yet after execution of apoptosis SELADIN-1 is cleaved at putative caspase cleavage sites and therefore is presumably inactivated. These results indicate that SELADIN-1 is an integral component of the cellular machinery protecting cells, in particular neurons, from oxidative stress. Once oxidative stress becomes overwhelming, SELADIN-1 becomes a target for caspase action in the course of apoptosis. *SELADIN-1* is a good candidate gene for therapeutical intervention to protect cells against degeneration and cell death. It is in particular, a good candidate gene for therapeutical intervention to protect neurons from Aβ induced cytotoxicity.

EXAMPLE I

Post-mortem Alzheimer´s disease brain tissues

Brain tissues from Alzheimer´s disease patients and control subjects were removed within 6 hours of death, and immediately frozen on dry ice. Parallel sections were fixed in formaldehyde for histopathological confirmation of the diagnosis and for cell counts. Brain areas with massive neuronal cell loss as well as areas with largely preserved neurons were identified for comparisons of gene expression and stored at -80°C until RNA extractions were performed.

Identification of *SELADIN-1* by differential display PCR

Total RNA from post-mortem brain tissues was prepared by using the RNeasy kit (Qiagen). The RNA preparations were treated with DNase I (Boehringer Mannheim) together with RNAsin (Promega) for 30 minutes, followed by phenol extraction, and ethanol precipitation. 0.2 mg of each RNA preparation were transcribed to cDNA by using Expand Reverse Transcriptase (Boehringer Mannheim) with one base ancor primers $HT_{11}A$, $HT_{11}C$ and $HT_{11}G$. In the following PCR reaction, the cDNAs were amplified by using $HT_{11}A$ along with the random primers HAP-5 (5'-TGCCGAAGCTTGGAGCTT-3') and HAP3-T (5'TGCCGAAGCTTTGGTCAT-3'). Taq-polymerase (AmpliTaq, Perkin Elmer Corp.), dGTP, dCTP, and dTTP (Amersham Pharmacia Biotech) and (α^{35}S)-dATP (NEN life science products) were used in a PCR protocol according to Zhao et al. The PCR products were separated on 6% polyacrylamide-urea sequencing gels that were dried subsequently on 3 mm filter paper (Whatman), and X-ray films (Dupont) were exposed for 12 hours.

Cloning and sequencing

Differential bands were excised from the gel, boiled in water for 10 minutes, centrifuged, and cDNAs were precipitated from the supernatant fluids by using ethanol and glycogen/sodiumacetate, followed by dialysis against 10% glycerol for 1 hour through 0.025 mm filters (type VS, Millipore). The dialysates were used as templates for the reamplification reactions that were done under identical conditions as in the differential

display PCR, with the exception of the initial cycle for nonspecific annealing. The resulting PCR products were separated by agarose gelelectrophoresis, purified from the gel with the QIAEXII Agarose Gel Extraction Kit (Qiagen), and cloned into the *Hind* III restriction site of pBluescript KS (Stratagene). Cloned cDNA fragments were sequenced with an ABI 377 DNA sequencer (Perkin Elmer Corp.) by using T3 and T7 primers.

Amplification of a *SELADIN-1* cDNA-fragment

A *SELADIN-1* cDNA fragment was amplified by using cDNA transcribed from human brain tissue by using RNA High Fidelity Taq-polymerase (Boehringer Mannheim) and *SELADIN-1*-specific primers for a PCR reaction with 40 cycles of annealing of 70 °C for 1 minute, and polymerization at 72 °C for 3 minutes. The PCR products were separated by agarose gel electrophoresis, purified, and cloned into the *Sma* I restriction site of pBluescript KS (Stratagene). The cloned PCR product was sequenced, and restriction were used as a probe both for screening a human brain cDNA library and for probing Northern blots.

Northern blotting

Total RNA from post-mortem human brains were prepared by using the Trizol reagent (Gibco BRL, Life Technologies), following the manufacturer's instructions. 5 - 10 mg of RNA were separated in 1 % formaldehyde-containing agarose gels, and the RNA was blotted onto nylon membranes (Hybond-N^+, Amersham). Membranes were hybridized with (α-^{32}P)-dCTP (NEN) labeled *SELADIN-1*-specific cDNA probes that were generated by using the Megaprime DNA labelling kit (Amersham). Membranes were washed under high stringency conditions, and X-ray films were exposed for 1 to 72 hours. To control for equal loading of RNA, the identical membranes were probed with a 700 pb cDNA fragment of human glycerolaldehyd-3-phosphate dehydrogenase (*GAPDH*), or with a b-actin cDNA fragment (Clontech).

In situ hybridization

Several *SELADIN-1*-specific cDNA probes of 650bp and of 900bp representing the initial two parts of the open reading frame were cloned in pBluescript (Stratagene) and reversely transcribed in the presence of ^{35}S-CTP by using the Ambion transcription kit. In situ hybridization was done with, 14mm sections of adult rat brain cut on a cryomicrotome, mounted on aminoalkylsilane-treated slides and fixed in 4 % paraformaldehyde in PBS for 5 min at room temperature. After washing for 5 min in PBS, sections were acetylated for 10 min, passed through a series of increasing ethanol grades and air dried. Prehybridizations were done in 50 % deionized formamide, 25 mM EDTA, 25 mM Pipes, pH 6.8, 0.75 M NaCl, 0.2 % SDS, 5 x Denhardt's, 10 mM DTT, 250 mg/ml denatured herring sperm DNA and 250 mg/ml yeast tRNA. Hybridization of slides with RNA sense and antisense probes diluted to 2000 – 5000 cpm/ml in the same buffer with additional 10 % dextransulphate was performed at 50 °C for 12 hours. Slides were then washed four times in 4 x SCC for 5 min. each, followed by an incubation for 30 min. at 37 °C with 40 mg/ml RNAseA in 0.5 M NaCl, 10 mM Tris-HCL, pH 7.5, 1mM EDTA and another 30 min without RNAseA. Then slides were washed twice for 15 min. at 50 °C in 2 x SCC and dried through graded ethanols. Slides were exposed to Kodak Biomax x-ray films for 15 days and subsequently dipped in Kodak NTB-3 nuclear track emulsion and exposed for 6 weeks. After developing in Kodak D19 and fixing in Kodak Unifix, slides were counterstained with Mayer" Hemalaun and coversplipped.

Recombinant expression of SELADIN-1-EGFP fusion proteins in tissue culture

The complete coding region of *SELADIN-1* was subcloned into the N-terminus of the pEGFP-N1-expression vector (Clontech). Cos-7-cells were transfected with *EGFP* or with *SELADIN-1-EGFP* by using the SuperFect transfection reagent from Qiagen according to the manufacturers instructions. Cells were cultured in 3 cm dishes for two days. Part of the cells were stained for the Golgi-apparatus with 0.25 mM BODIPY TR ceramide (molecular probes) for one hour, the other part was treated with 250 nM of the mitochondrial stain Mito Tracker Red CM-H2Xros (Molecular probes) for 45 min. the subcellular localization of the SELADIN-1-EGFP fusion protein was analyzed by confocal laser scanning microscopy using the appropriate filter sets.

CLAIMS

1. An isolated nucleic acid encoding a protein molecule shown in SEQ ID NO. 1.

2. An isolated nucleic acid molecule encoding a protein molecule, the function of which is to protect cells against degeneration and/or cell death, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof.

3. An isolated nucleic acid molecule of claim 1 or 2, wherein the nucleic acid molecule is a D N A molecule.

4. An isolated nucleic acid molecule of claim 3, wherein the nucleic acid molecule is a cD N A molecule, in particular a cD N A molecule comprising a nucleotide sequence shown in SEQ ID NO. 2.

5. An isolated D N A molecule capable of hybridizing with the complement of the cD N A described in SEQ ID NO. 2 under stringent condition.

6. An isolated D N A molecule of claim 5 encoding a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

7. An isolated nucleic acid molecule of claim 2 or 5 encoding a protein molecule, the function of which is to protect cells of the nerve system, muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, lung, trachea or placenta against degeneration and/or cell death.

8. A vector comprising a nucleic acid molecule according to one of claims 1 to 7.

9. A vector according to claim 8 wherein said vector is a plasmid, a virus or a bacteriophage.

10. A plasmid according to claim 9 wherein said plasmid is adapted for expression in a yeast cell and further comprises the regulatory elements necessary for expression of said nucleic acid molecule.

11. A plasmid according to claim 9 wherein said plasmid is adapted for expression in a bacterial cell and further comprises the regulatory elements necessary for expression of said nucleic acid molecule.

12. A plasmid according to claim 8 wherein said plasmid is adapted for expression in a mammalian cell and further comprises the regulatory elements necessary for expression of said nucleic acid molecule.

13. A cell transformed with a nucleic acid molecule according to one of claims 1 to 7, wherein said cell is in particular a bacterial cell, a yeast cell, a mammalian cell, or an insect cell.

14. A protein molecule shown in SEQ ID NO.1.

15. A protein molecule, the function of which is to protect cells against degeneration and/or cell death, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof.

16. A protein molecule of claim 14, the function of which is to protect cells of the nerve system, muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, against degeneration and/or cell death.

17. An antibody specifically immunoreactive with an immunogen, wherein said immunogen is a protein molecule shown in SEQ ID NO. 1.

18. An antibody specifically immunoreactive with a protein molecule, the function of which is to protect cells against degeneration and/or cell death, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO. 1 or a functional variant thereof.

19. A method of detecting pathological cells in a subject which comprises immunocytochemically staining cells with an antibody of claim 17 or 18, wherein a low degree of staining in said cell compared to a cell representing a known health status indicates a pathological change of said cells.

20. A method of claim 19, wherein cells of the nerve system, muscular system, prostate, stomach, testis, ovary, adrenal glands, mammary glands, liver, spleen, lung, trachea or placenta are used.

21. A method of diagnosing or prognosing a disease, in particular a neurological disease, in a subject comprising:

determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

(b) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

and comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby diagnosing or prognosing a disease, in particular a neurological disease, in said subject.

22. A method of monitoring the progression of a disease, in particular a neurological disease, in a subject, comprising:

determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

and comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby monitoring progression of a disease, in particular a neurological disease, in said subject.

23. A method of evaluating a treatment for a disease, in particular a neurological disease, in a subject, said method comprising:

determining a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

and comparing said level, or said activity, or both said level and said activity, of at least one of said substances (a) to (h) to a reference value representing a known disease or health status, thereby evaluating a treatment for a disease, in particular a neurological disease, in said subject.

24. The method according to one of claims 21 to 23, wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

25. The method according to one of claims 21 to 24, wherein a decrease of a level or an activity of (i) a transcription product of a D N A molecule encoding a protein molecule, the amino acid sequence of which comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof or (ii) a protein molecule, the amino acid sequence of which comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof, in a sample from said subject relative to a reference value representing a known health status indicates the presence of a disease, in particular a neurological disease, in said subject.

26. The method according to one of claims 21 to 25, wherein said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2

encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

27. The method according to one of claims 21 to 26, wherein said subject suffers from Alzheimer's disease or related neurofibrillary disorders, or neurodegenerative states characterized by cell degeneration or cell death, or Parkinson's disease, or Huntington disease, or Amyotrophic lateralsclerosis or Pick's disease.

28. An agent which affects an activity, or level, or both said activity and level, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f).

29. An agent of claim 28, wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

30. An agent of claim 28 or 29 wherein said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

31. A medicament comprising an agent according to one of claims 28 to 30.

32. Use of an agent for preparation of a medicament for treating or preventing a neurological disease, in particular Alzheimer's disease, which agent affects an activity, or level, or both said activity and level, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f).

33. Use of an agent according to claim 32, wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

34. Use of an agent according to claim 32 or 33, wherein said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

35. A method of identifying an agent that affects an activity, or level, or both said activity and level, of at least one substance which is selected from the group consisting of

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

comprising the steps of:

(i) providing a sample containing at least one substance which is selected from the group consisting of (a) to (f),

(ii) contacting said sample with at least one agent,

(iii) comparing an activity, or level, or both said activity and level, of at least one of said substances before and after contacting.

36. A method of claim 35 wherein the function of said protein molecule or a variant thereof is to protect cells from degeneration and/or cell death.

37. A method of claim 35 or 36 wherein said D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 encodes a protein molecule, the function of which is to protect cells against degeneration and/or cell death.

38. A kit for diagnosis, or prognosis of a disease, said kit comprising:

(1) at least one reagent which is selected from the group consisting of reagents that selectively detect

(a) a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(b) a transcription product of a D N A molecule encoding a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(c) a protein molecule, wherein the amino acid sequence of the protein molecule comprises the sequence shown in SEQ ID NO.1 or a functional variant thereof,

(d) a D N A molecule capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(e) a transcription product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(f) a translation product of a D N A molecule, wherein said D N A molecule is capable of hybridizing with the complement of the c D N A described in SEQ ID NO. 2 under stringent conditions,

(g) a molecule affecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (f),

(h) a molecule which is affected in its level, or its activity, or both its level and activity, by at least one substance which is selected from the group consisting of (a) to (f),

(2) instructions for diagnosing, or prognosing said disease by

(i) detecting a level, or an activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) in a sample from said subject;

and

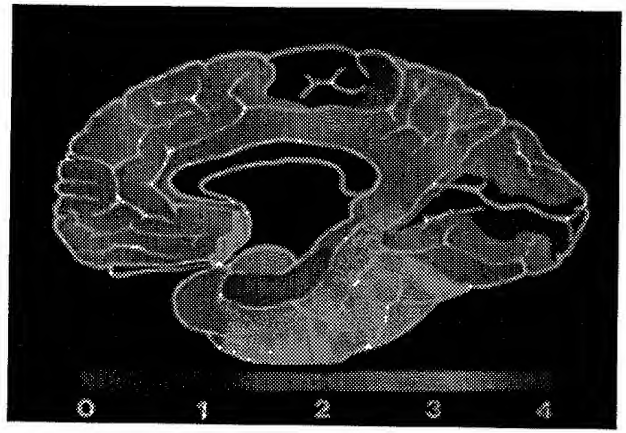
(ii) diagnosing, or prognosing said disease, wherein

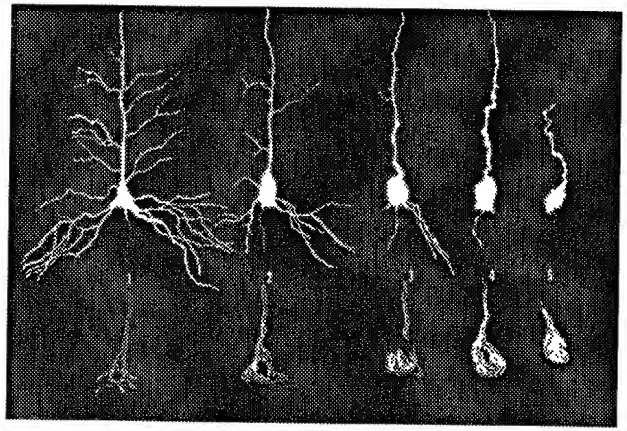
a varied level, or activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) compared to a reference value representing a known health status;

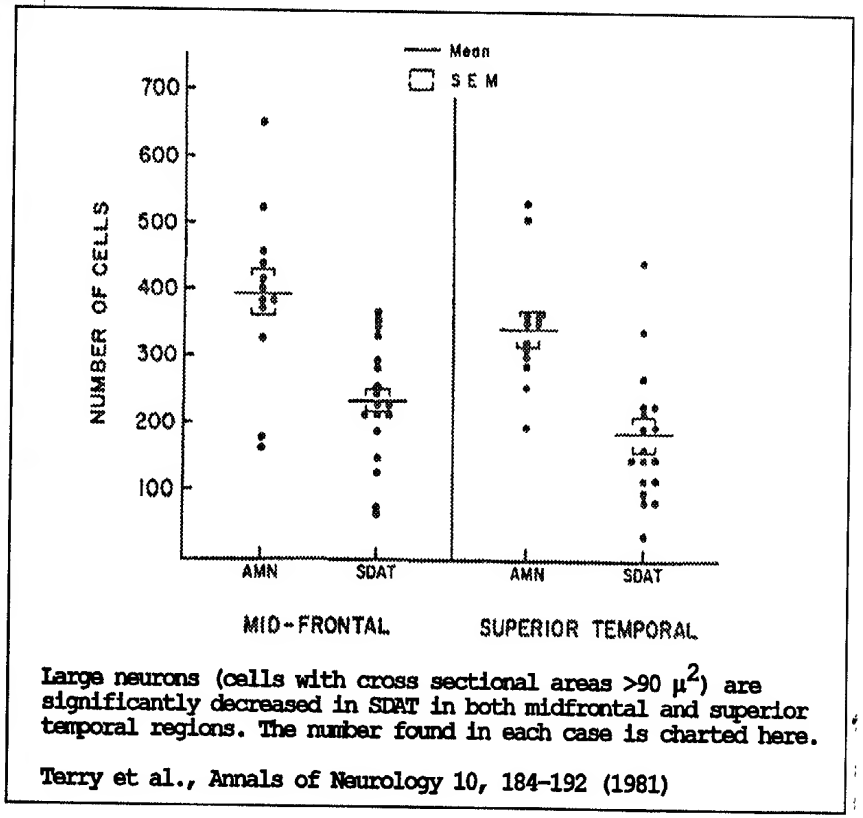
or a level, or activity, or both said level and said activity, of at least one substance which is selected from the group consisting of (a) to (h) similar or equal to a

reference value representing a known disease status indicates diagnosis, or prognosis of said disease.

Selective vulnerability of brain regions in Alzheimer´s disease





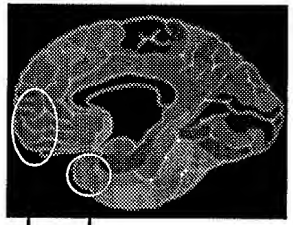


Large neurons (cells with cross sectional areas >90 μ^2) are significantly decreased in SDAT in both midfrontal and superior temporal regions. The number found in each case is charted here.

Terry et al., Annals of Neurology 10, 184-192 (1981)

Figure 1

Identification of genes differentially expressed in AD brain regions



extract RNA

RT → oligo-dT-primer

cDNA pool

PCR → random primer
oligo-dT primer
α^{35}S dATP

Polyacrylamide-sequencing-gel

- cut out differentially expressed bands
- reamplify eluted cDNAs
- cloning and sequencing
- expression analysis
- functional analysis

Figure 2

Identification of genes differentially expressed in AD brain regions

Material: AD brain tissue

post mortem time intervall <6h

2 different regions histologically characterized

- inferior temporal lobe
- frontal cortex

Method: mRNA differential display screen

Figure 3

Expression of Seladin-1 in AD brain

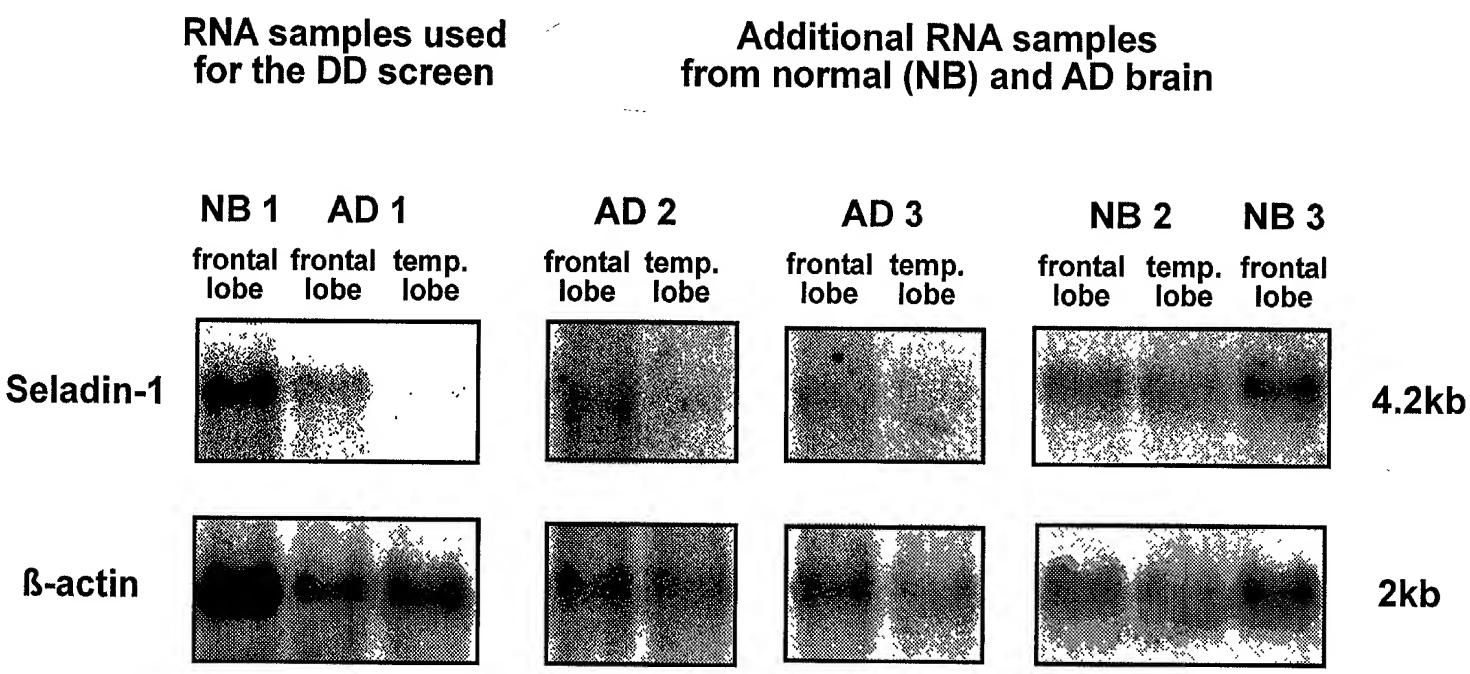


Figure 4

Expression of Seladin-1 in different human brain regions

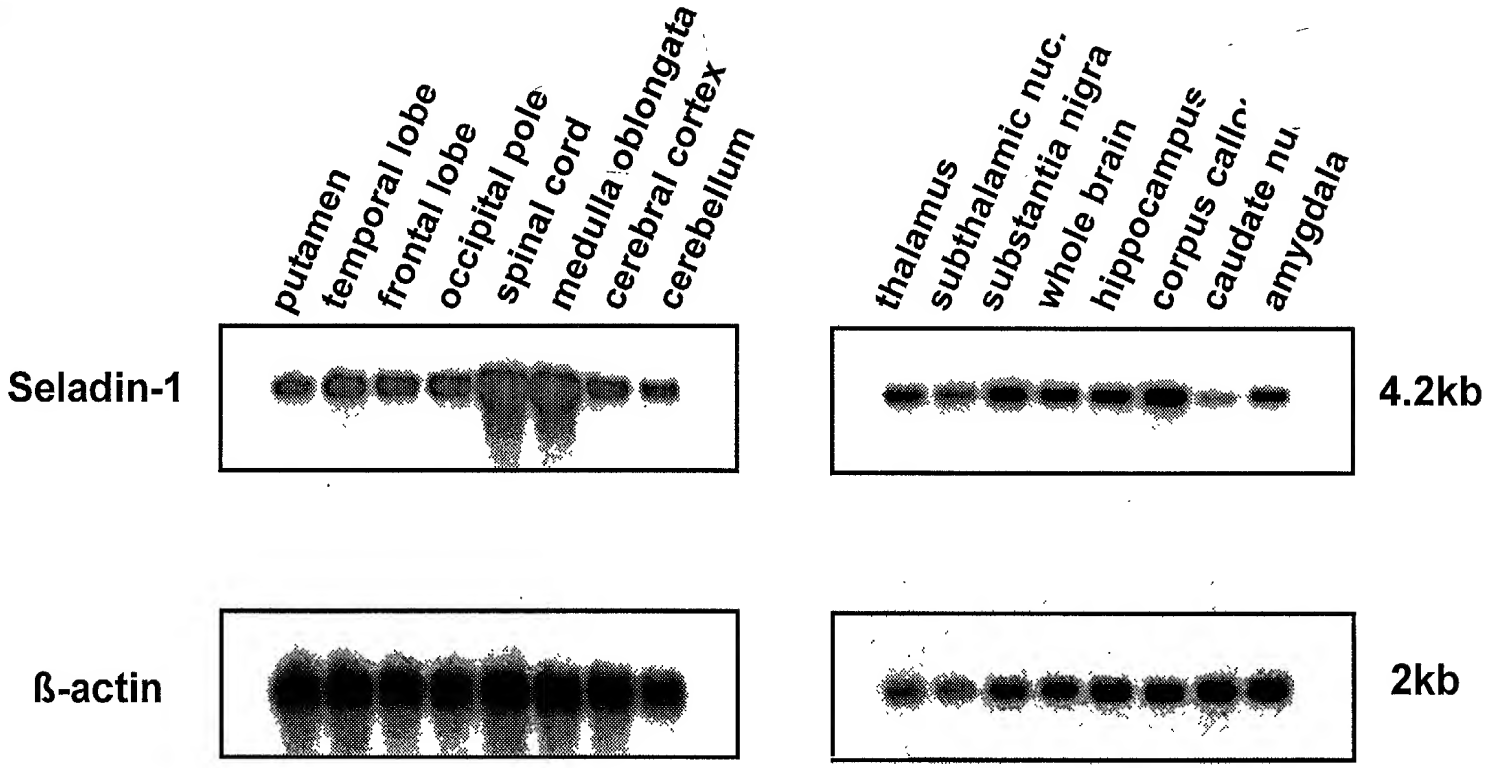
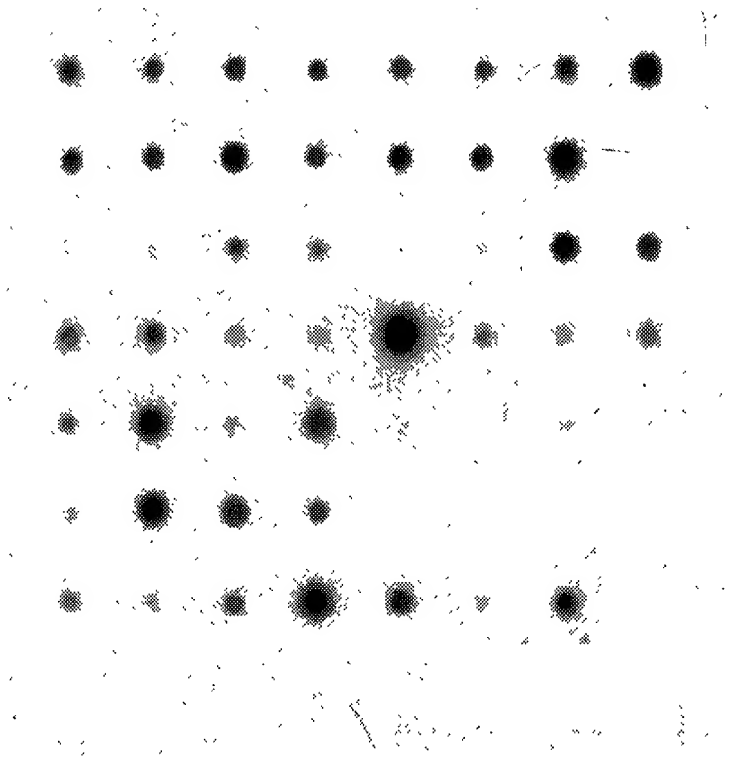


Figure 5

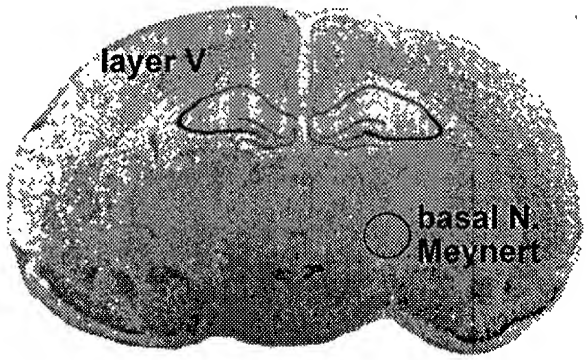
Expression of Seladin-1 in human tissues

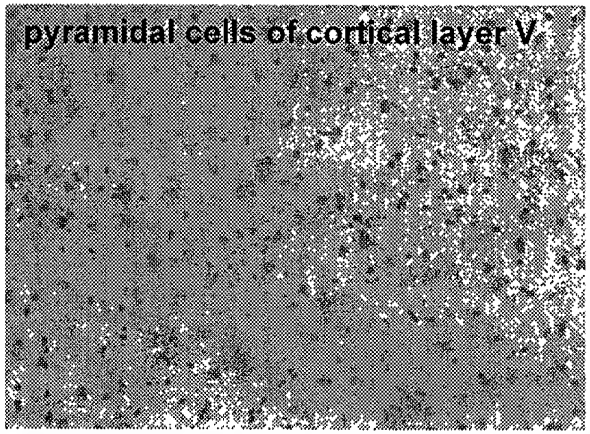


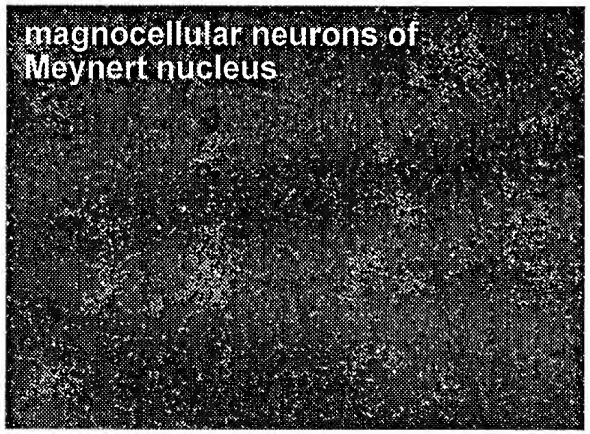
whole brain	amyg-dala	caudate nucleus	cere-bellum	cerebral cortex	frontal lobe	hippo-campus	medulla oblong-ata
occipital lobe	putamen	sub-stantia nigra	temporal lobe	thalamus	sub-thalamic nucleus	spinal cord	
heart	aorta	skeletal muscle	colon	bladder	uterus	prostate	stomach
testis	ovary	pancreas	pituitary gland	adrenal gland	thyroid gland	salivary gland	mam-mary gland
kidney	liver	small intestine	spleen	thymus	periphe-ral leuko-cyte	lymph node	bone marrow
appendix	lung	trachea	placenta				
fetal brain	fetal heart	fetal kidney	fetal liver	fetal spleen	fetal thymus	fetal lung	
yeast total RNA 100ng	yeast tRNA 100ng	E. coli rRNA 100ng	E. coli DNA 100ng	Poly r(A) 100ng	human Cot1DNA 100ng	human DNA 100ng	human DNA 500ng

Figure 6

Expression of Seladin-1 in rat brain







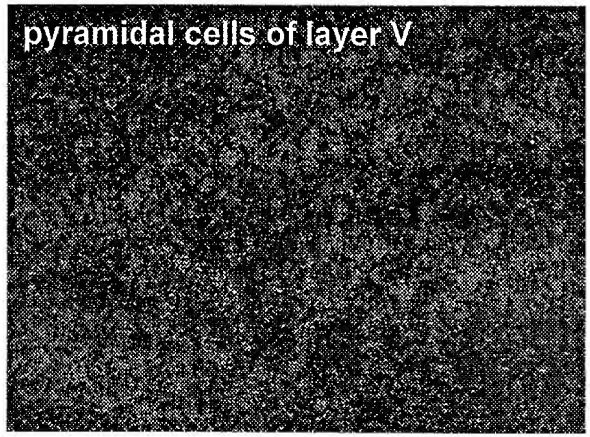


Figure 7

Expression of Seladin-1 in rat brain

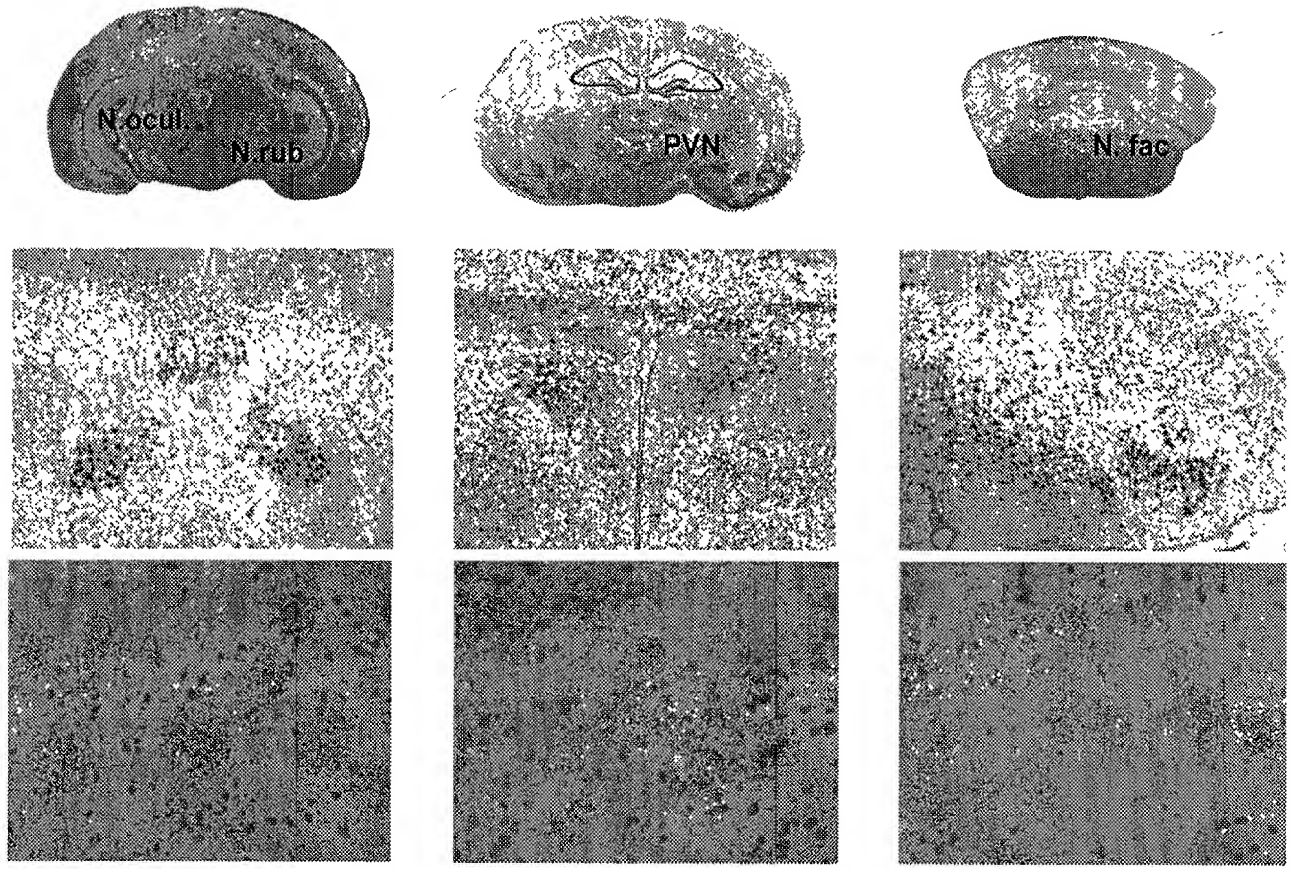
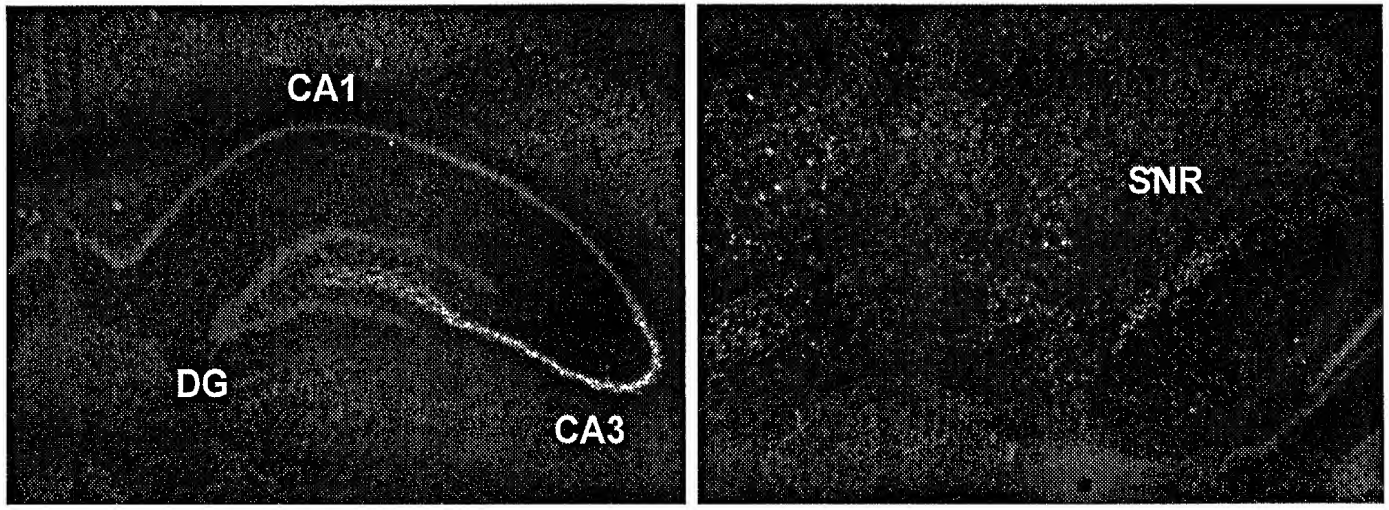


Figure 8

Expression of Seladin-1 in rat brain



hippocampus substantia nigra

Figure 9

Subcellular localization of Seladin-1 EGFP fusionprotein

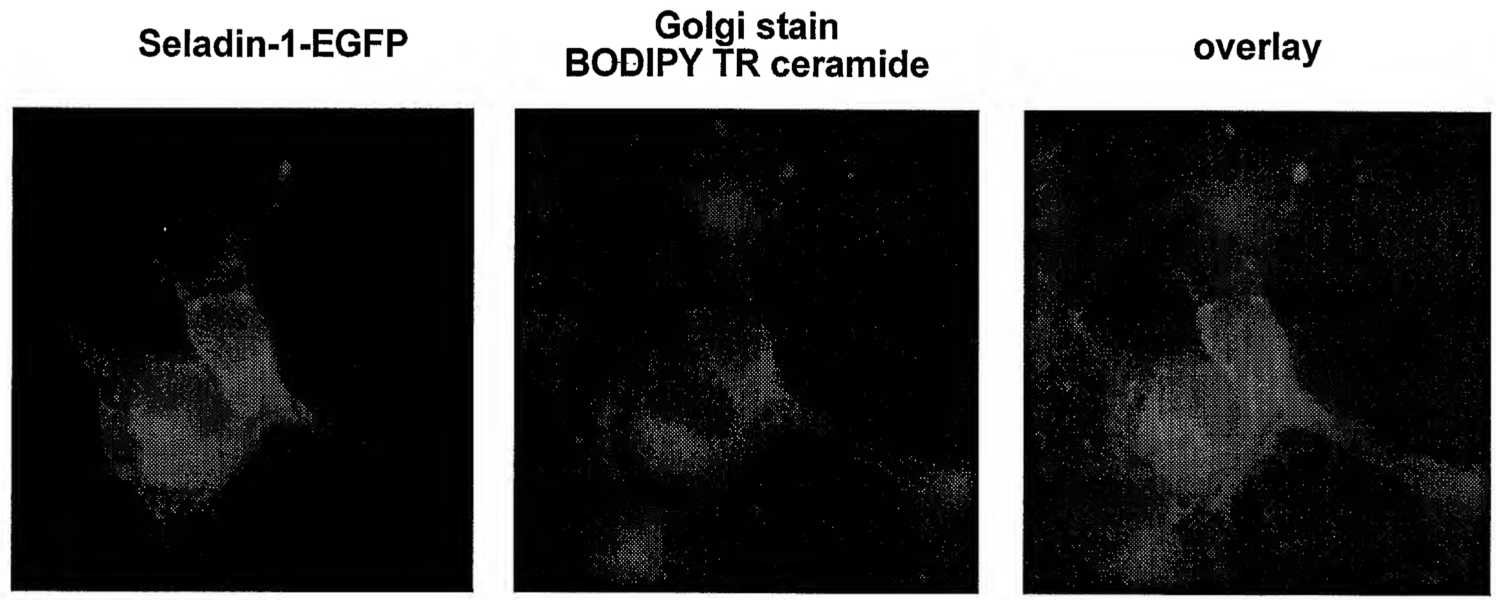


Figure 10

Subcellular localization of Seladin-1 EGFP fusionprotein

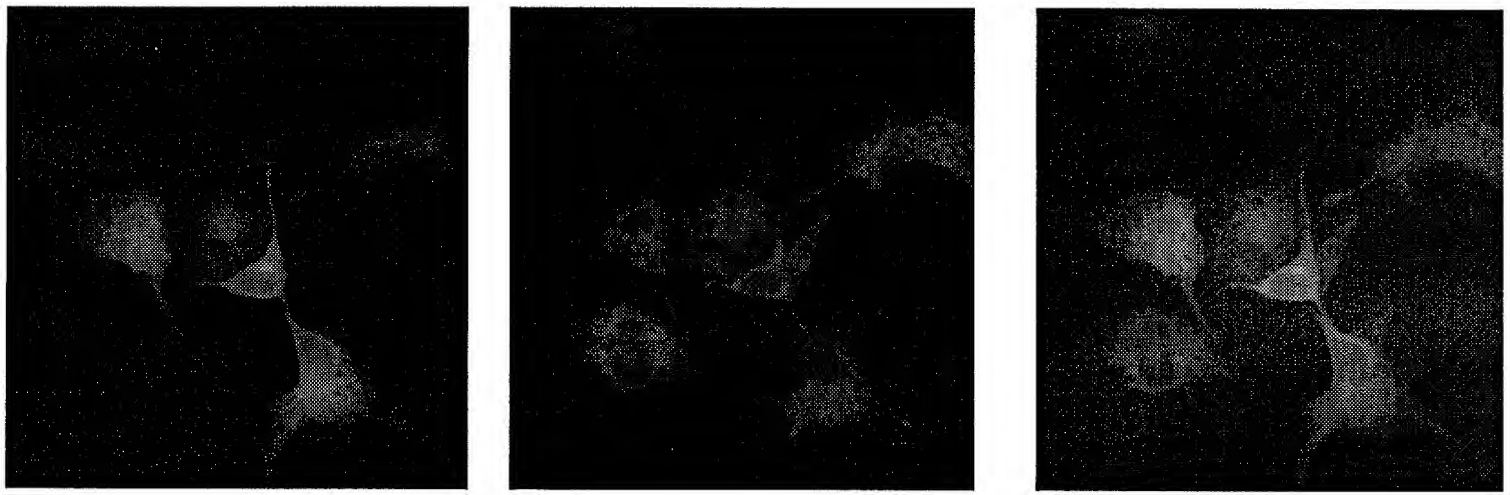
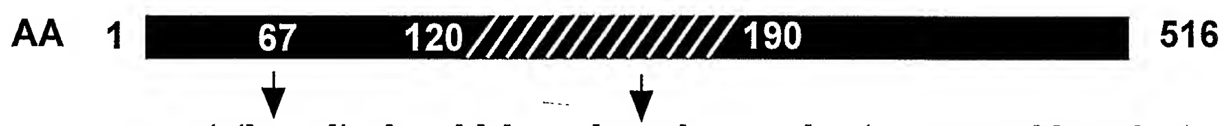
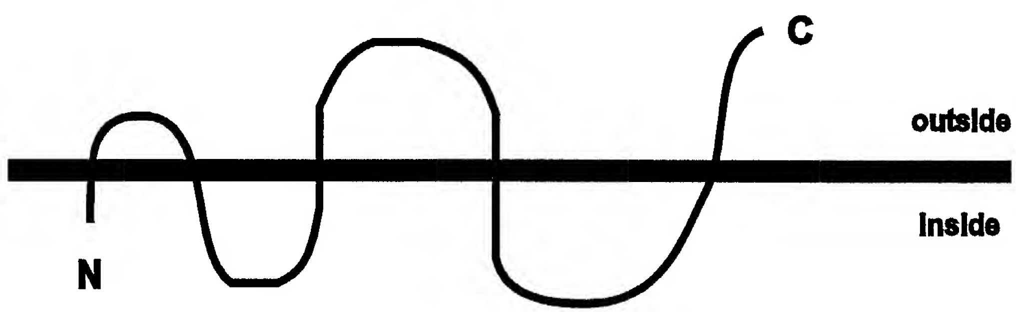


Figure 11

Multiple sequence alignments and secondary structure prediction of Seladin-1



- putative mitochondrial targeting sequence
- homology region to many oxido-reductases
  e.g. L-gulono-gamma-lactone-oxidase
  6-hydroxy-d-nicotine oxidase
  D-lactate dehydrogenase
- contains oxygen oxidoreductases covalent FAD binding site



- 5 possible transmembrane regions

Figure 12

FIGURE 13: SEQ ID NO.1

Seladin-1 amino acid sequence

Seladin-1.orf Length: 516 May 29, 1998 14:51 Type: P
Check: 1354 ..

```
1    MEPAVSLAVC ALLFLLWVRL KGLEFVLIHQ RWVFVCLFLL PLSLIFDIYY
51   YVRAWVVFKL SSAPRLHEQR VRDIQKQVRE WKEQGSKTFM CTGRPGWLTV
101  SLRVGKYKKT HKNIMINLMD ILEVDTKKQI VRVEPLVTMG QVTALLTSIG
151  WTLPVLPELD DLTVGGLIMG TGIESSSHKY GLFQHICTAY ELVLADGSFV
201  RCTPSENSDL FYAVPWSCGT LGFLVAAEIR IIPAKKYVKL RFEPVRGLEA
251  ICAKFTHESQ RQENHFVEGL LYSLDEAVIM TGVMTDEAEP SKLNSIGNYY
301  KPWFFKHVEN YLKTNREGLE YIPLRHYYHR HTRSIFWELQ DIIPFGNNPI
351  FRYLFGWMVP PKISLLKLTQ GETLRKLYEQ HHVVQDMLVP MKCLQQALHT
401  FQNDIHVYPI WLCPFILPSQ PGLVHPKGNE AELYIDIGAY GEPRVKHFEA
451  RSCMRQLEKF VRSVHGFQML YADCYMNREE FWEMFDGSLY HKLREKLGCQ
501  DAFPEVYDKI CKAARH
```

FIGURE 14: SEQ ID NO.2

Seladin-1 cDNA sequence

Seladin-1 Length: 4248 April 28, 1998 14:10 Type: N Check: 8184 ..

```
   1  cccgggctgt gggctacagg cgcagagcgg gccaggcgcg gagctggcgg
  51  cagtgacagg aggcgcgaac ccgcagcgct taccgcgcgg cgccgcacca
 101  tggagcccgc cgtgtcgctg gccgtgtgcg cgctgctctt cctgctgtgg
 151  gtgcgcctga aggggctgga gttcgtgctc atccaccagc gctgggtgtt
 201  cgtgtgcctc ttcctcctgc cgctctcgct tatcttcgat atctactact
 251  acgtgcgcgc ctgggtggtg ttcaagctca gcagcgctcc gcgcctgcac
 301  gagcagcgcg tgcgggacat ccagaagcag gtgcgggaat ggaaggagca
 351  gggtagcaag accttcatgt gcacggggcg ccctggctgg ctcactgtct
 401  cactacgtgt cgggaagtac aagaagacac acaaaaacat catgatcaac
 451  ctgatggaca ttctggaagt ggacaccaag aaacagattg tccgtgtgga
 501  gcccttggtg accatgggcc aggtgactgc cctgctgacc tccattggct
 551  ggactctccc cgtgttgcct gagcttgatg acctcacagt ggggggcttg
 601  atcatgggca caggcatcga gtcatcatcc cacaagtacg gcctgttcca
 651  acacatctgc actgcttacg agctggtcct ggctgatggc agctttgtgc
 701  gatgcactcc gtccgaaaac tcagacctgt tctatgccgt accctggtcc
 751  tgtgggacgc tgggtttcct ggtggccgct gagatccgca tcatccctgc
 801  caagaagtac gtcaagctgc gtttcgagcc agtgcggggc ctggaggcta
 851  tctgtgccaa gttcacccac gagtcccagc ggcaggagaa ccacttcgtg
 901  gaagggctgc tctactccct ggatgaggct gtcattatga caggggtcat
 951  gacagatgag gcagagccca gcaagctgaa tagcattggc aattactaca
1001  agccgtggtt ctttaagcat gtggagaact atctgaagac aaaccgagag
1051  ggcctggagt acattccctt gagacactac taccaccgcc acacgcgcag
1101  catcttctgg gagctccagg acatcatccc ctttggcaac aaccccatct
1151  tccgctacct ctttggctgg atggtgcctc ccaagatctc cctcctgaag
1201  ctgacccagg gtgagaccct gcgcaagctg tacgagcagc accacgtggt
1251  gcaggacatg ctggtgccca tgaagtgcct gcagcaggcc ctgcacacct
1301  tccaaaacga catccacgtc taccccatct ggctgtgtcc gttcatcctg
1351  cccagccagc caggcctagt gcaccccaaa ggaaatgagg cagagctcta
```

1401 catcgacatt ggagcatatg gggagccgcg tgtgaaacac tttgaagcca

1451 ggtcctgcat gaggcagctg gagaagtttg tccgcagcgt gcatggcttc

1501 cagatgctgt atgccgactg ctacatgaac cgggaggagt tctgggagat

1551 gtttgatggc tccttgtacc acaagctgcg agagaagctg ggttgccagg

1601 acgccttccc cgaggtgtac gacaagatct gcaaggccgc caggcactga

1651 gctggagccc gcctggagag acagacacgt gtgagtggtc aggcatcttc

1701 ccttcactca agcttggctg ctttcctaga tccacacttt caaagagaaa

1751 cccctccaga actcccaccc tgacagccca acaccacctt cctcctggct

1801 tccaggggggc agcccagtgg aatggaaaga atgtgggatt tggagtcaga

1851 caagcctgag tccagttccc cgtttagaac tcattagctg tgtgactctg

1901 ggtgagtccc ttaacccctc tgagcccggg tctcttcatt agttgaaagg

1951 gatagtaata cctacttgca ggttgttgtc atctgagttg agcactggtc

2001 acattgaagg tgctgggtaa gtggtagctc ttgttgcttc ccgttcagcg

2051 tcacatctgc agtggagcct gaaaaggctc cacattaggt cacctgtgca

2101 cagccatggc tggaatgatg aaggggatac gctggagttg ccctgccatc

2151 gcctccatca gccagacgag gtcctcacag gagaaggaca gctcttcccc

2201 accctgggat ctcaggaggg cagccacgga gtggggaggc cccagatgcg

2251 ctgtgccaaa gccaggtccg aggccaaagt tctccctgcc atccttggtg

2301 ccgtcctgcc ccttcctcct tcatgcctgg gcctgcaggc ccaccccagc

2351 caccactgag tccactcgga gtgccctgtg ttcctggaga aggcattcca

2401 gggttgaatc ttgtcccagc ctcagcctgg gacacctagg tggagagagt

2451 ggtctccgct ctgaattgga tccaggggac ctgggctcat tcttcttggc

2501 tcaccaaccc tgcaggcctc atctttccca aaacccactt tgtcttggtg

2551 ggagtgggtc cgcgctgctc tgcagcaggg gctggggagt ggacagcatc

2601 aggtgggaaa gtggagtcca ccctcatgtt tctgtaggat tctcaccgtg

2651 gggctggaag aaaagagcat cgacttgatt tctccaacca ctcatccctc

2701 tttttctttc ttccaccact ccccacccca gctgtagtta atttcagtgc

2751 cttacaaatc ctaagctcag agaaagttcc atttccgttc cagagggaag

2801 ggaacctccc taggtccttc cctggcttgt tataacgcaa agcttggttg

2851 tttatgcaac tctatcttaa gaactgccca gcctcagctg aaaacccgaa

2901 tctgagaagg aattgcgtca tgtaagggaa gctggaatta agggagctga

2951 gccagtcatg gttgtggcgt gtgagtcagg agacctaggt ttcagcccct

3001 ctctactgtc agcgagctgt gcaacgtggg caagtcattg tcctctgagc

3051 tgcagtttcc tcatctgtca catcgctaca gacaagacct ccctggaacc

3101 cttctgattg tcttagacac tgtggttgca aaacccacgg aaagcctcat

3151 ttgtgtggaa agtcagagga aaaatgatcc agtggacact tggggattat

3201 ctgtcattca agatccttcc ttcaacccca aggccagctc ccatctcatt

3251 tccagaaagg ctcatacctg gcttgcaggg aagcatctgt cttgtcattc

3301 caggtgccag aatcctctca gagtcattga agggtgttca cccatcccac

3351 ccaaggcttg gcacactgcc agtgtcttag cagggtcttg tgagggctgg

3401 gggcatccag gcactcagaa ggcaaaggaa ccaccctacc catttggcct

3451 ctggaggggg cagaagaaag aaagaaacct catcctatat tttacaaagc

3501 atgtgaattc tggcattagc tctcatagga gacccatgtg cttccttgct

3551 cagtgcaaaa ctgatgattc tacttgctgt agatgaatgg ttaacacgag

3601 ctagttaaac agtgccattg ttttgccagt gaagcctcca accctaagcc

3651 actgggacgg tggccagaga tgccagcagc ctctgtcgcc cttagtcata

3701 taaccaaaat ccagacctta tccacaaccc ggggcttgga aaggaaggta

3751 ttttggaatc acaccctccg gttatgttgc tccagtaaaa tcttgcctgg

3801 aaagaggcag tcttcttagc atggtgagct gagttcatgg ctttttttg

3851 tagccagtcc tgtccctggc catccatgtg atggttttgg atggagttaa

3901 acttgatgcc agtgggcagt gcatgtggaa agtatcagag taagcctctc

3951 ccctccagag ccctgagttt cttggctgca tgaaggtttt ctttagaatc

4001 agaattgtag ccagtttctt tggccagaag gatgaatact tggatattac

4051 tgaaagggag gggtggagat gggtgtggca gtgtatggtg tgtgattttt

4101 attttcttct ttggtcatgg gggccaagga gaaaggcatg aatcttccct

4151 gtcaggctct tacagccaca ggcactgtgt ctactgtctg gaagacatgt

4201 ccccgtggct gtggggccgc tgcttctgtt taaataaaag tggcctgg

FIGURE 15 CDNA sequence comparison KIAA0018/Seladin-1

```
    1 ggcgcgaacccgcagcgcttaccgcgcggcgccgcaccatggagcccgcc 50
      ||||||||||||||||||||||||||||||||||||||||||||||||||
   62 ggcgcgaacccgcagcgcttaccgcgcggcgccgcaccatggagcccgcc 111

   51 gtgtcgctggccgtgtgcgcgctgctcttcctgctgtgggtgcgcctgaa 100
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  112 gtgtcgctggccgtgtgcgcgctgctcttcctgctgtgggtgcgcctgaa 161

  101 ggggctggagttcgtgctcatccaccagcgctgggtgttcgtgtgcctct 150
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  162 ggggctggagttcgtgctcatccaccagcgctgggtgttcgtgtgcctct 211

  151 tcctcctgccgctctcgcttatcttcgatatctactactacgtgcgcgcc 200
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  212 tcctcctgccgctctcgcttatcttcgatatctactactacgtgcgcgcc 261

  201 tgggtggtgttcaagctcagcagcgctccgcgcctgcacgagcagcgcgt 250
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  262 tgggtggtgttcaagctcagcagcgctccgcgcctgcacgagcagcgcgt 311

  251 gcgggacatccagaagcaggtgcgggaatggaaggagcagggtagcaaga 300
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  312 gcgggacatccagaagcaggtgcgggaatggaaggagcagggtagcaaga 361

  301 ccttcatgtgcacggggcgccctggctggctcactgtctcactacgtgtc 350
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  362 ccttcatgtgcacggggcgccctggctggctcactgtctcactacgtgtc 411

  351 gggaagtacaagaagacacacaaaaacatcatgatcaacctgatggacat 400
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  412 gggaagtacaagaagacacacaaaaacatcatgatcaacctgatggacat 461

  401 tctggaagtggacaccaagaaacagattgtccgtgtggagcccttggtga 450
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  462 tctggaagtggacaccaagaaacagattgtccgtgtggagcccttggtga 511

  451 ccatgggccaggtgactgccctgctgacctccattggctggactctcccc 500
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  512 ccatgggccaggtgactgccctgctgacctccattggctggactctcccc 561

  501 gtgttgcctgagcttgatgacctcacagtgggggggcttgatcatgggcac 550
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  562 gtgttgcctgagcttgatgacctcacagtgggggggcttgatcatgggcac 611

  551 aggcatcgagtcatcatcccacaagtacggcctgttccaacacatctgca 600
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  612 aggcatcgagtcatcatcccacaagtacggcctgttccaacacatctgca 661

  601 ctgcttacgagctggtcctggctgatggcagctttgtgcgatgcactccg 650
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  662 ctgcttacgagctggtcctggctgatggcagctttgtgcgatgcactccg 711

  651 tccgaaaactcagacctgttctatgccgtaccctggtcctgtgggacgct 700
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  712 tccgaaaactcagacctgttctatgccgtaccctggtcctgtgggacgct 761

  701 gggtttcctggtggccgctgagatccgcatcatccctgccaagaagtacg 750
      ||||||||||||||||||||||||||||||||||||||||||||||||||
  762 gggtttcctggtggccgctgagatccgcatcatccctgccaagaagtacg 811
```

```
751 tcaagctgcgtttcgagccagtgcggggcctggaggctatctgtgccaag 800
    ||||||||||||||||||||||||||||||||||||||||||||||||||
812 tcaagctgcgtttcgagccagtgcggggcctggaggctatctgtgccaag 861

801 ttcacccacgagtcccagcggcaggagaaccacttcgtggaagggctgct 850
    ||||||||||||||||||||||||||||||||||||||||||||||||||
862 ttcacccacgagtcccagcggcaggagaaccacttcgtggaagggctgct 911

851 ctactccctggatgaggctgtcattatgacaggggtcatgacagatgagg 900
    ||||||||||||||||||||||||||||||||||||||||||||||||||
912 ctactccctggatgaggctgtcattatgacaggggtcatgacagatgagg 961

901 cagagcccagcaagctgaatagcattggcaattactacaagccgtggttc 950
    ||||||||||||||||||||||||||||||||||||||||||||||||||
962 cagagcccagcaagctgaatagcattggcaattactacaagccgtggttc 1011

951 tttaagcatgtggagaactatctgaagacaaaccgagagggcctggagta 1000
    ||||||||||||||||||||||||||||||||||||||||||||||||||
1012 tttaagcatgtggagaactatctgaagacaaaccgagagggcctggagta 1061

1001 cattcccttgagacactactaccaccgccacacgcgcagcatcttctggg 1050
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1062 cattcccttgagacactactaccaccgccacacgcgcagcatcttctggg 1111

1051 agctccaggacatcatccccctttggcaacaaccccatcttccgctacctc 1100
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1112 agctccaggacatcatccccctttggcaacaaccccatcttccgctacctc 1161

1101 tttggctggatggtgcctcccaagatctccctcctgaagctgacccaggg 1150
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1162 tttggctggatggtgcctcccaagatctccctcctgaagctgacccaggg 1211

1151 tgagaccctgcgcaag.tgtacgagcagcaccacgtggtgcaggacatgc 1199
     |||||||||||||||| ||||||||||||||||||||||||||||||||
1212 tgagaccctgcgcaagctgtacgagcagcaccacgtggtgcaggacatgc 1261

1200 tggtgcccatgaagtgcctgcagcaggccctgcacaccttccaaaacgac 1249
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1262 tggtgcccatgaagtgcctgcagcaggccctgcacaccttccaaaacgac 1311

1250 atccacgtctaccccatctggctgtgtccgttcatcctgcccagccagcc 1299
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1312 atccacgtctaccccatctggctgtgtccgttcatcctgcccagccagcc 1361

1300 aggcctagtgcaccccaaaggaaatgaggcagagctctacatcgacattg 1349
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1362 aggcctagtgcaccccaaaggaaatgaggcagagctctacatcgacattg 1411

1350 gagcatatggggagccgcgtgtgaaacactttgaagccaggtcctgcatg 1399
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1412 gagcatatggggagccgcgtgtgaaacactttgaagccaggtcctgcatg 1461

1400 aggcagctggagaagtttgtccgcagcgtgcatggcttccagatgctgta 1449
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1462 aggcagctggagaagtttgtccgcagcgtgcatggcttccagatgctgta 1511

1450 tgccgactgctacatgaaccgggaggagttctgggagatgtttgatggct 1499
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1512 tgccgactgctacatgaaccgggaggagttctgggagatgtttgatggct 1561

1500 ccttgtaccacaagctgcgagagaagctgggttgccaggacgccttcccc 1549
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1562 ccttgtaccacaagctgcgagagaagctgggttgccaggacgccttcccc 1611
```

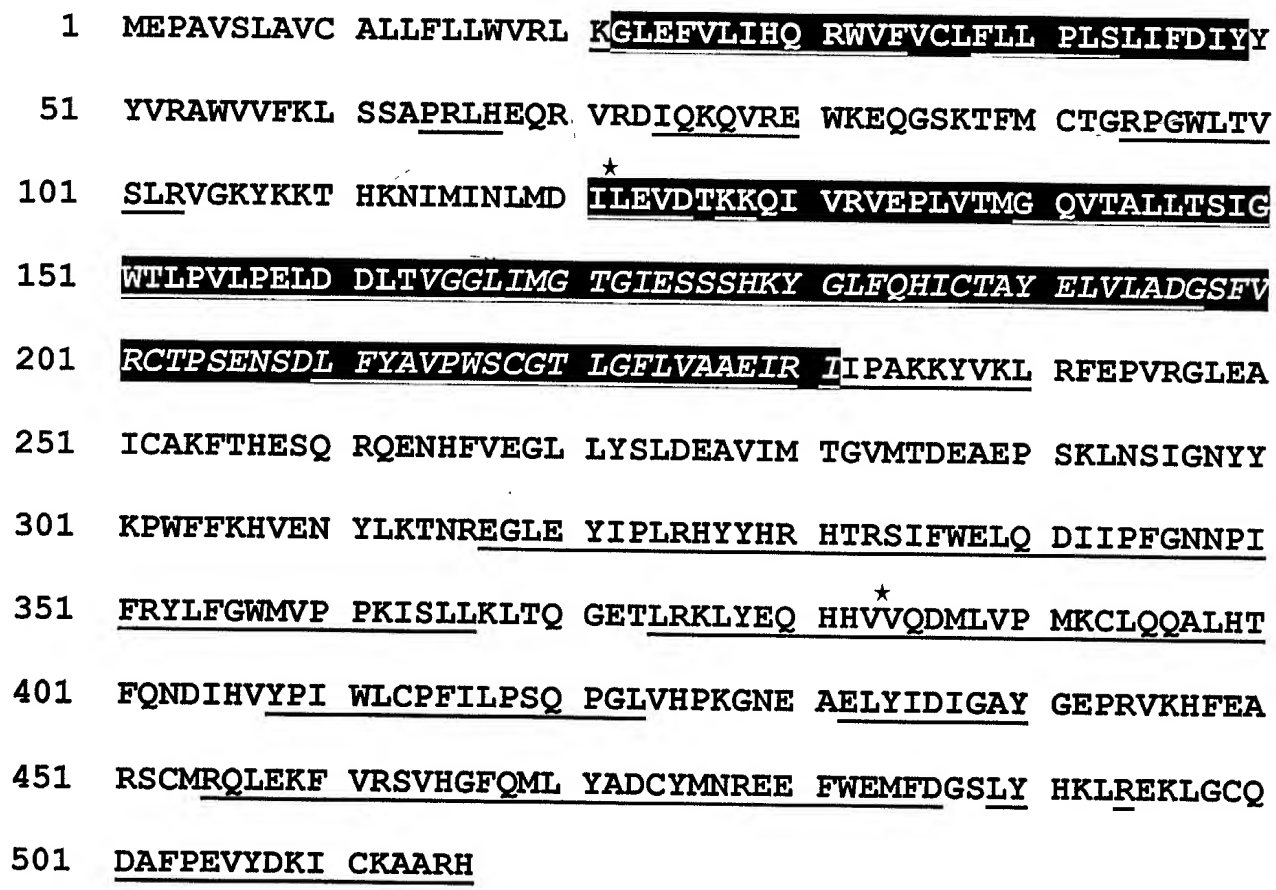
```
1550 gaggtgtacgacaagatctgcaaggccgccaggcactgagctggagcccg 1599
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1612 gaggtgtacgacaagatctgcaaggccgccaggcactgagctggagcccg 1661

1600 cctggagagacagacacgtgtgagtggtcaggcatcttcccttcactcaa 1649
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1662 cctggagagacagacacgtgtgagtggtcaggcatcttcccttcactcaa 1711

1650 gcttggctgctttcctagatccacactttcaaagagaaaccccctccagaa 1699
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1712 gcttggctgctttcctagatccacactttcaaagagaaaccccctccagaa 1761

1700 ctcccaccctgacagcccaacaccaccttcctcctggcttccaggggcca 1749
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1762 ctcccaccctgacagcccaacaccaccttcctcctggcttccaggggcca 1811

1750 gcccagtggaatggaaagaatgtgggatttggagtcagacaagcctgagt 1799
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1812 gcccagtggaatggaaagaatgtgggatttggagtcagacaagcctgagt 1861

1800 ccagttccccgtttagaactcattagctgtgtgactctgggtgagtccct 1849
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1862 ccagttccccgtttagaactcattagctgtgtgactctgggtgagtccct 1911

1850 taacccctctgagcccgggtctcttcattagttgaaagggatagtaatac 1899
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1912 taacccctctgagcccgggtctcttcattagttgaaagggatagtaatac 1961

1900 ctacttgcaggttgttgtcatctgagttgagcactggtcacattgaaggt 1949
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1962 ctacttgcaggttgttgtcatctgagttgagcactggtcacattgaaggt 2011

1950 gctgggtaagtggtagctcttgttgcttcccgttcagcgtcacatctgca 1999
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2012 gctgggtaagtggtagctcttgttgcttcccgttcagcgtcacatctgca 2061

2000 gtggagcctgaaaaggctccacattaggtcacctgtgcacagccatggct 2049
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2062 gtggagcctgaaaaggctccacattaggtcacctgtgcacagccatggct 2111

2050 ggaatgatgaaggggatacgctggagttgccctgccatcgcctccatcag 2099
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2112 ggaatgatgaaggggatacgctggagttgccctgccatcgcctccatcag 2161

2100 ccagacgaggtcctcacaggagaaggacagctcttccccaccctgggatc 2149
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2162 ccagacgaggtcctcacaggagaaggacagctcttccccaccctgggatc 2211

2150 tcaggagggcagccacggagtggggaggccccagatgcgctgtgccaaag 2199
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2212 tcaggagggcagccacggagtggggaggccccagatgcgctgtgccaaag 2261

2200 ccaggtccgaggccaaagttctccctgccatccttggtgccgtcctgccc 2249
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2262 ccaggtccgaggccaaagttctccctgccatccttggtgccgtcctgccc 2311

2250 cttcctccttcatgcctgggcctgcaggcccaccccagccaccactgagt 2299
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2312 cttcctccttcatgcctgggcctgcaggcccaccccagccaccactgagt 2361

2300 ccactcggagtgccctgtgttcctggagaaggcattccagggttgaatct 2349
     ||||||||||||||||||||||||||||||||||||||||||||||||||
2362 ccactcggagtgccctgtgttcctggagaaggcattccagggttgaatct 2411
```

```
2350 tgtcccagcctcagcctgggacacctaggtggagagagtggtctccgctc 2399
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2412 tgtcccagcctcagcctgggacacctaggtggagagagtggtctccgctc 2461

2400 tgaattggatccaggggacctgggctcattcttcttggctcaccaaccct 2449
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2462 tgaattggatccaggggacctgggctcattcttcttggctcaccaaccct 2511

2450 gcaggcctcatctttcccaaaacccactttgtcttggtgggagtgggtcc 2499
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2512 gcaggcctcatctttcccaaaacccactttgtcttggtgggagtgggtcc 2561

2500 gcgctgctctgcagcaggggctggggagtggacagcatcaggtgggaaag 2549
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2562 gcgctgctctgcagcaggggctggggagtggacagcatcaggtgggaaag 2611

2550 tggagtccaccctcatgtttctgtaggattctcaccgtggggctggaaga 2599
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2612 tggagtccaccctcatgtttctgtaggattctcaccgtggggctggaaga 2661

2600 aaagagcatcgacttgatttctccaaccactcatccctctttttctttct 2649
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2662 aaagagcatcgacttgatttctccaaccactcatccctctttttctttct 2711

2650 tccaccactccccaccccagctgtagttaatttcagtgccttacaaatcc 2699
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2712 tccaccactccccaccccagctgtagttaatttcagtgccttacaaatcc 2761

2700 taagctcagagaaagttccatttccgttccagagggaagggaacctccct 2749
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2762 taagctcagagaaagttccatttccgttccagagggaagggaacctccct 2811

2750 aggtccttccctggcttgttataacgcaaagcttggttgtttatgcaact 2799
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2812 aggtccttccctggcttgttataacgcaaagcttggttgtttatgcaact 2861

2800 ctatcttaagaactgcccagcctcagctgaaaacccgaatctgagaagga 2849
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2862 ctatcttaagaactgcccagcctcagctgaaaacccgaatctgagaagga 2911

2850 attgcgtcatgtaagggaagctggaattaagggagctgagccagtcatgg 2899
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2912 attgcgtcatgtaagggaagctggaattaagggagctgagccagtcatgg 2961

2900 ttgtggcgtgtgagtcaggagacctaggtttcagcccctctctactgtca 2949
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
2962 ttgtggcgtgtgagtcaggagacctaggtttcagcccctctctactgtca 3011

2950 gcgagctgtgcaacgtgggcaagtcattgtcctctgagctgcagtttcct 2999
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3012 gcgagctgtgcaacgtgggcaagtcattgtcctctgagctgcagtttcct 3061

3000 catctgtcacatcgctacagacaagacctccctggaacccttctgattgt 3049
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3062 catctgtcacatcgctacagacaagacctccctggaacccttctgattgt 3111

3050 cttagacactgtggttgcaaaacccacggaaagcctcatttgtgtggaaa 3099
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3112 cttagacactgtggttgcaaaacccacggaaagcctcatttgtgtggaaa 3161

3100 gtcagaggaaaaatgatccagtggacacttggggattatctgtcattcaa 3149
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3162 gtcagaggaaaaatgatccagtggacacttggggattatctgtcattcaa 3211
```

```
3150 gatccttccttcaaccccaaggccagctcccatctcatttccagaaaggc 3199
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3212 gatccttccttcaaccccaaggccagctcccatctcatttccagaaaggc 3261

3200 tcatacctggcttgcagggaagcatctgtcttgtcattccaggtgccaga 3249
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3262 tcatacctggcttgcagggaagcatctgtcttgtcattccaggtgccaga 3311

3250 atcctctcagagtcattgaagggtgttcacccatcccacccaaggcttgg 3299
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3312 atcctctcagagtcattgaagggtgttcacccatcccacccaaggcttgg 3361

3300 cacactgccagtgtcttagcagggtcttgtgagggctgggggcatccagg 3349
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3362 cacactgccagtgtcttagcagggtcttgtgagggctgggggcatccagg 3411

3350 cactcagaaggcaaaggaaccaccctacccatttggcctctggagggggc 3399
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3412 cactcagaaggcaaaggaaccaccctacccatttggcctctggagggggc 3461

3400 agaagaaagaaagaaacctcatcctatattttacaaagcatgtgaattct 3449
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3462 agaagaaagaaagaaacctcatcctatattttacaaagcatgtgaattct 3511

3450 ggcattagctctcataggagacccatgtgcttccttgctcagtgcaaaac 3499
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3512 ggcattagctctcataggagacccatgtgcttccttgctcagtgcaaaac 3561

3500 tgatgattctacttgctgtagatgaatggttaacacgagctagttaaaca 3549
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3562 tgatgattctacttgctgtagatgaatggttaacacgagctagttaaaca 3611

3550 gtgccattgttttgccagtgaagcctccaaccctaagccactgggacggt 3599
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3612 gtgccattgttttgccagtgaagcctccaaccctaagccactgggacggt 3661

3600 ggccagagatgccagcagcctctgtcgcccttagtcatataaccaaaatc 3649
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3662 ggccagagatgccagcagcctctgtcgcccttagtcatataaccaaaatc 3711

3650 cagaccttatccacaacccggggcttggaaaggaaggtattttggaatca 3699
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3712 cagaccttatccacaacccggggcttggaaaggaaggtattttggaatca 3761

3700 caccctccggttatgttgctccagtaaaatcttgcctggaaagaggcagt 3749
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3762 caccctccggttatgttgctccagtaaaatcttgcctggaaagaggcagt 3811

3750 cttcttagcatggtgagctgagttcatggctttttttgtagccagtcct 3799
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3812 cttcttagcatggtgagctgagttcatggctttttttgtagccagtcct 3861

3800 gtccctggccatccatgtgatggttttggatggagttaaacttgatgcca 3849
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3862 gtccctggccatccatgtgatggttttggatggagttaaacttgatgcca 3911

3850 gtgggcagtgcatgtggaaagtatcagagtaagcctctcccctccagagc 3899
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3912 gtgggcagtgcatgtggaaagtatcagagtaagcctctcccctccagagc 3961

3900 cctgagtttcttggctgcatgaaggttttctttagaatcagaattgtagc 3949
     ||||||||||||||||||||||||||||||||||||||||||||||||||||
3962 cctgagtttcttggctgcatgaaggttttctttagaatcagaattgtagc 4011
```

```
3950 cagtttctttggccagaaggatgaatacttggatattactgaaagggagg 3999
     ||||||||||||||||||||||||||||||||||||||||||||||||||
4012 cagtttctttggccagaaggatgaatacttggatattactgaaagggagg 4061

4000 ggtggagatgggtgtggcagtgtatggtgtgtgatttttatttcttctt 4049
     ||||||||||||||||||||||||||||||||||||||||||||||||||
4062 ggtggagatgggtgtggcagtgtatggtgtgtgatttttatttcttctt 4111

4050 tggtcatgggggccaaggagaaaggcatgaatcttccctgtcaggctctt 4099
     ||||||||||||||||||||||||||||||||||||||||||||||||||
4112 tggtcatgggggccaaggagaaaggcatgaatcttccctgtcaggctctt 4161

4100 acagccacaggcactgtgtctactgtctggaagacatgtccccgtggctg 4149
     ||||||||||||||||||||||||||||||||||||||||||||||||||
4162 acagccacaggcactgtgtctactgtctggaagacatgtccccgtggctg 4211

4150 tggggccgctgcttctgtttaaataaaagtggcctgg 4186
     ||||||||||||||||||||||||||||||||||||
4212 tggggccgctgcttctgtttaaataaaagtggcctgg 4248
```

Fig. 16



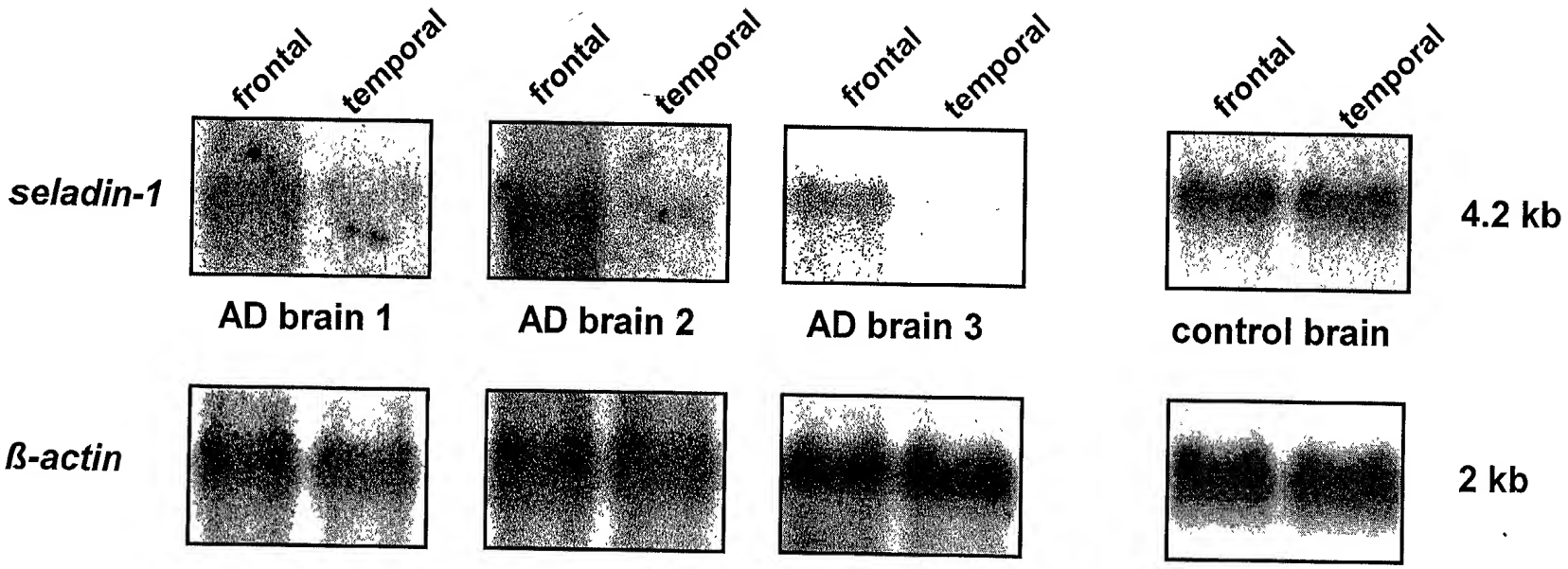

frontal
temporal
frontal
temporal
frontal
temporal
frontal
temporal
seladin-1
4.2 kb
AD brain 1
AD brain 2
AD brain 3
control brain
ß-actin
2 kb

Fig. 17 A

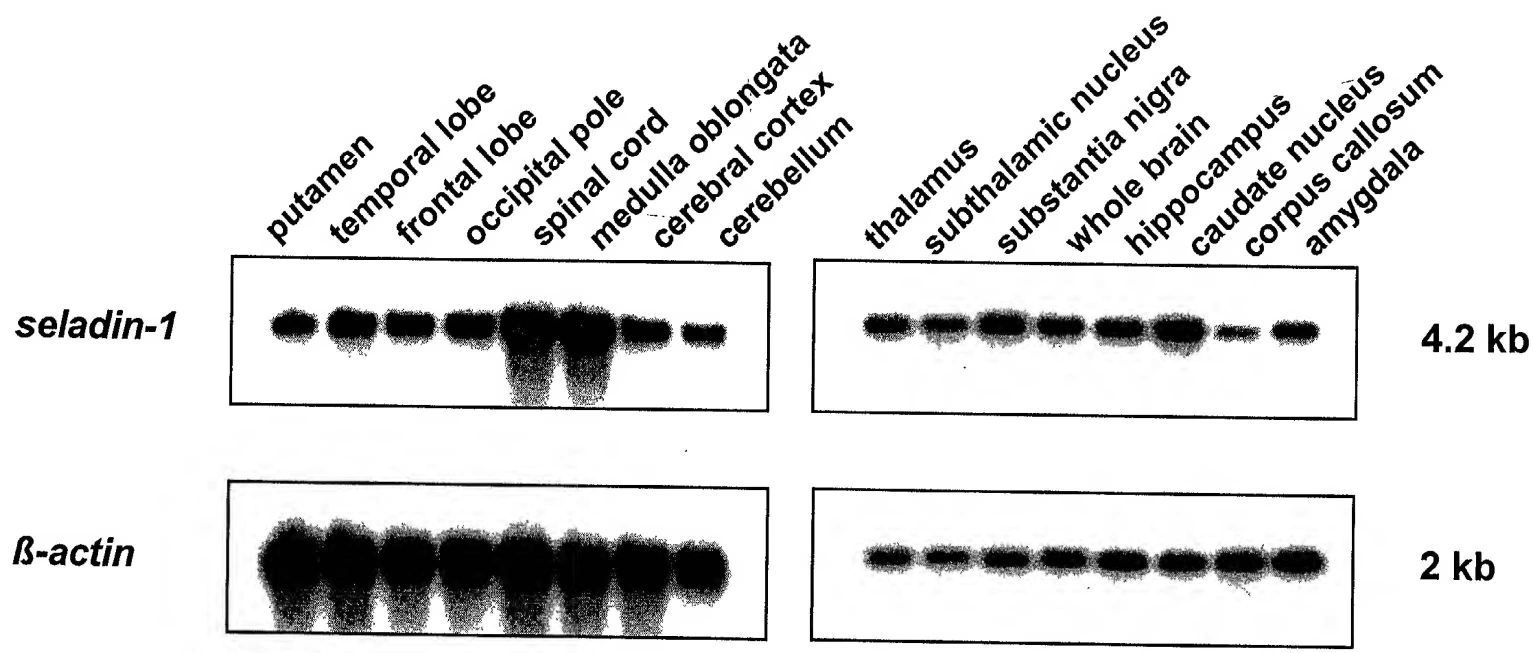

putamen
temporal lobe
frontal lobe
occipital pole
spinal cord
medulla oblongata
cerebral cortex
cerebellum
thalamus
subthalamic nucleus
substantia nigra
whole brain
hippocampus
caudate nucleus
corpus callosum
amygdala
seladin-1
ß-actin
4.2 kb
2 kb

Fig. 17 B

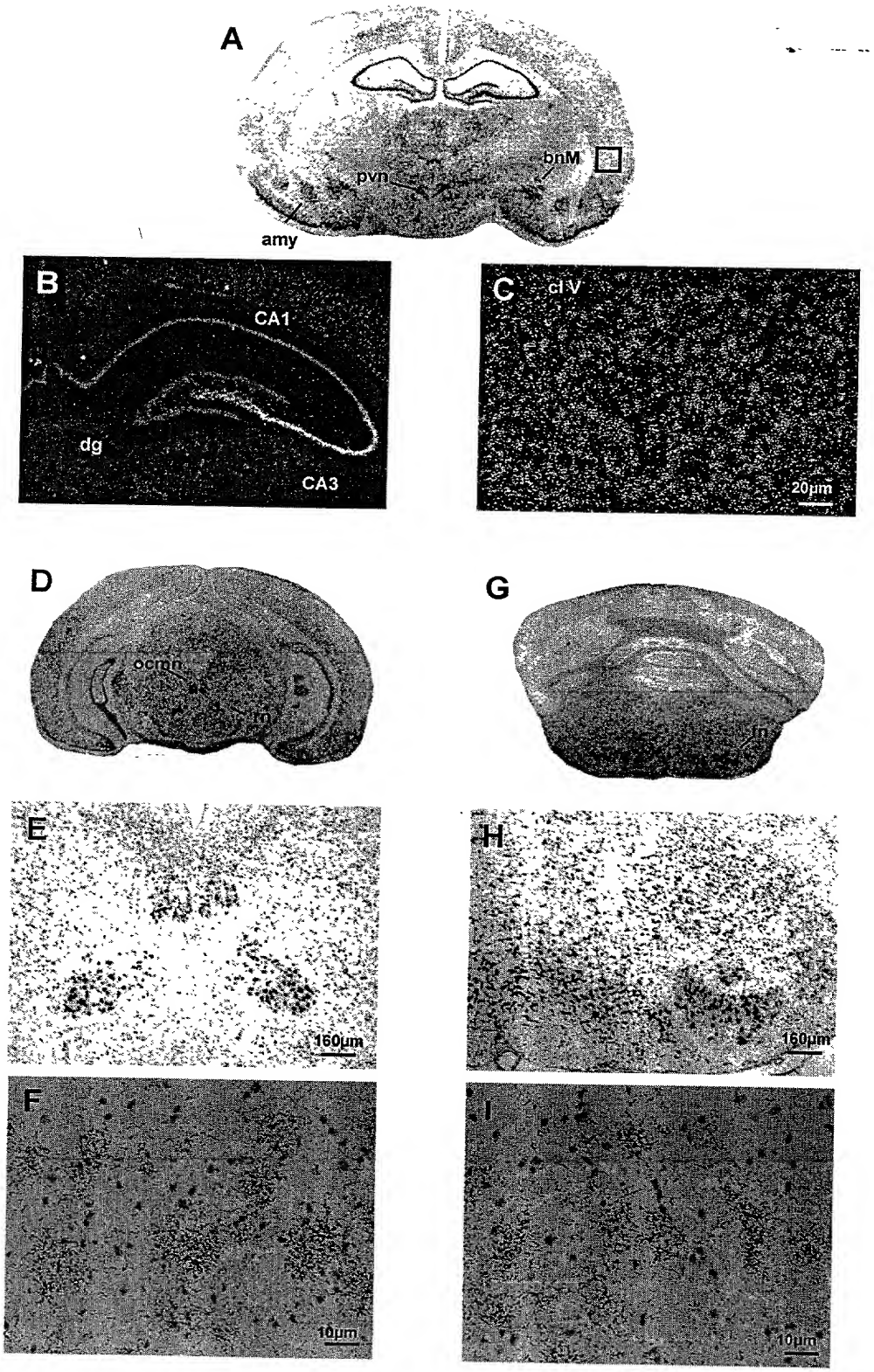


Fig. 18

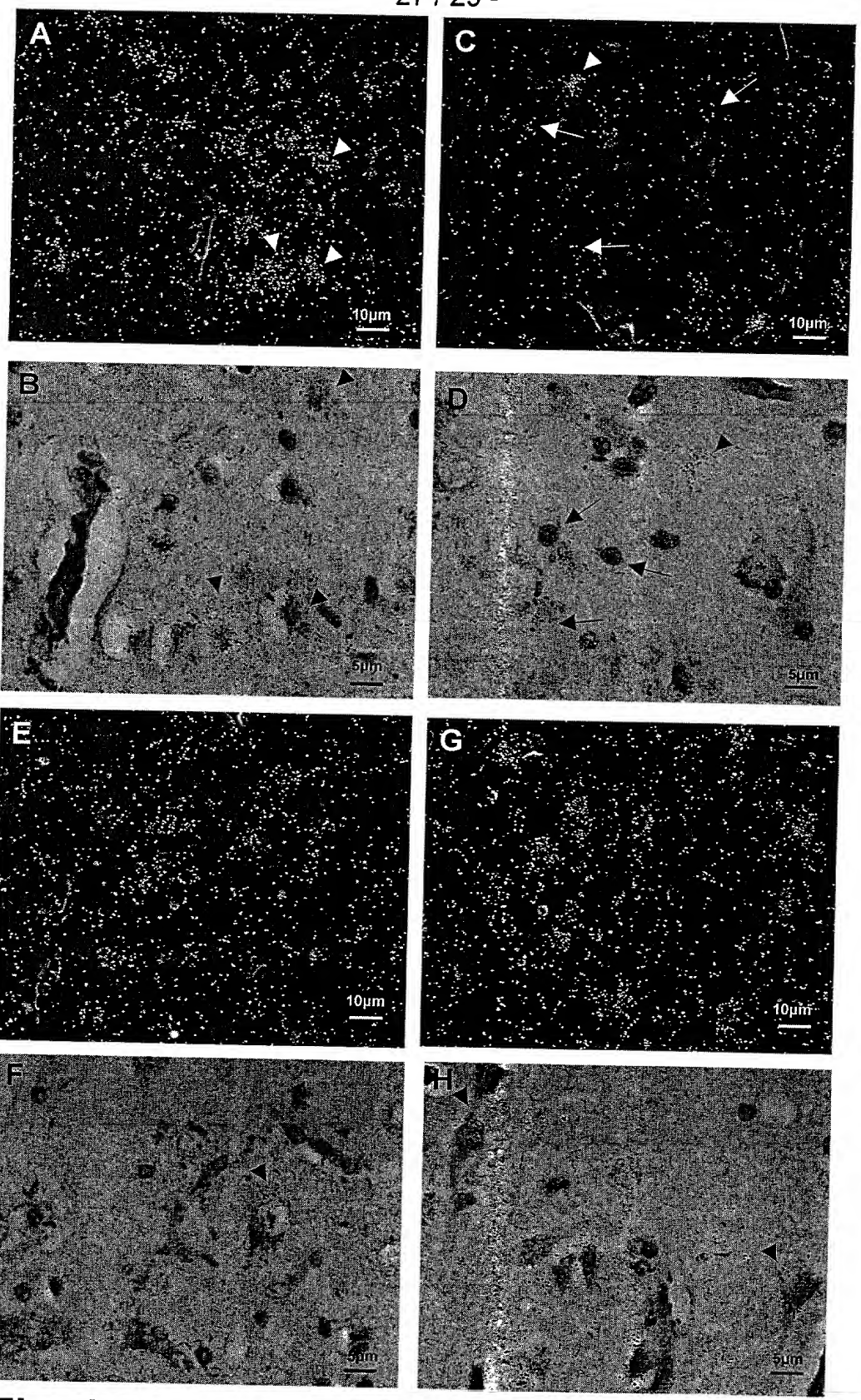


Fig. 19

09/831754

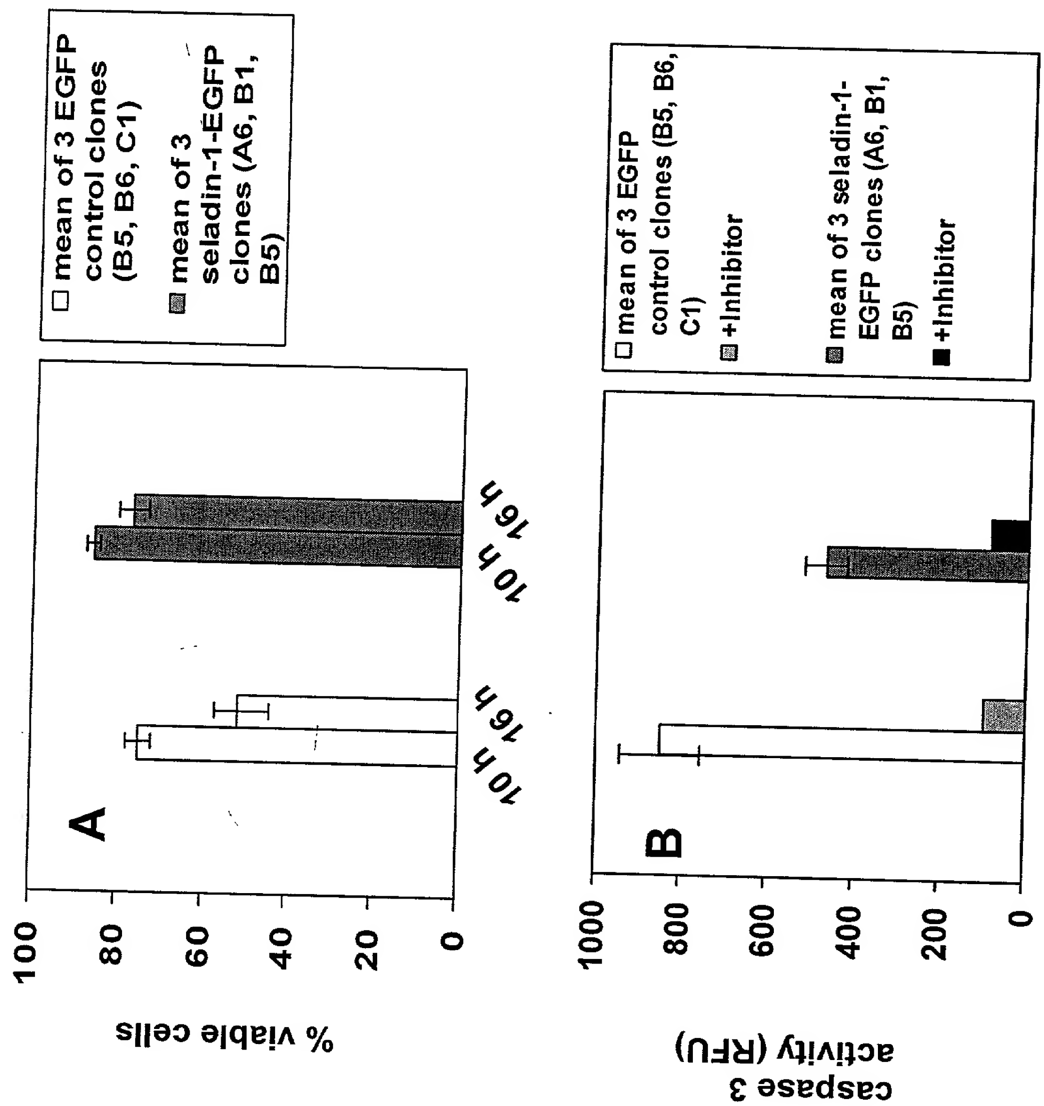


Fig. 20

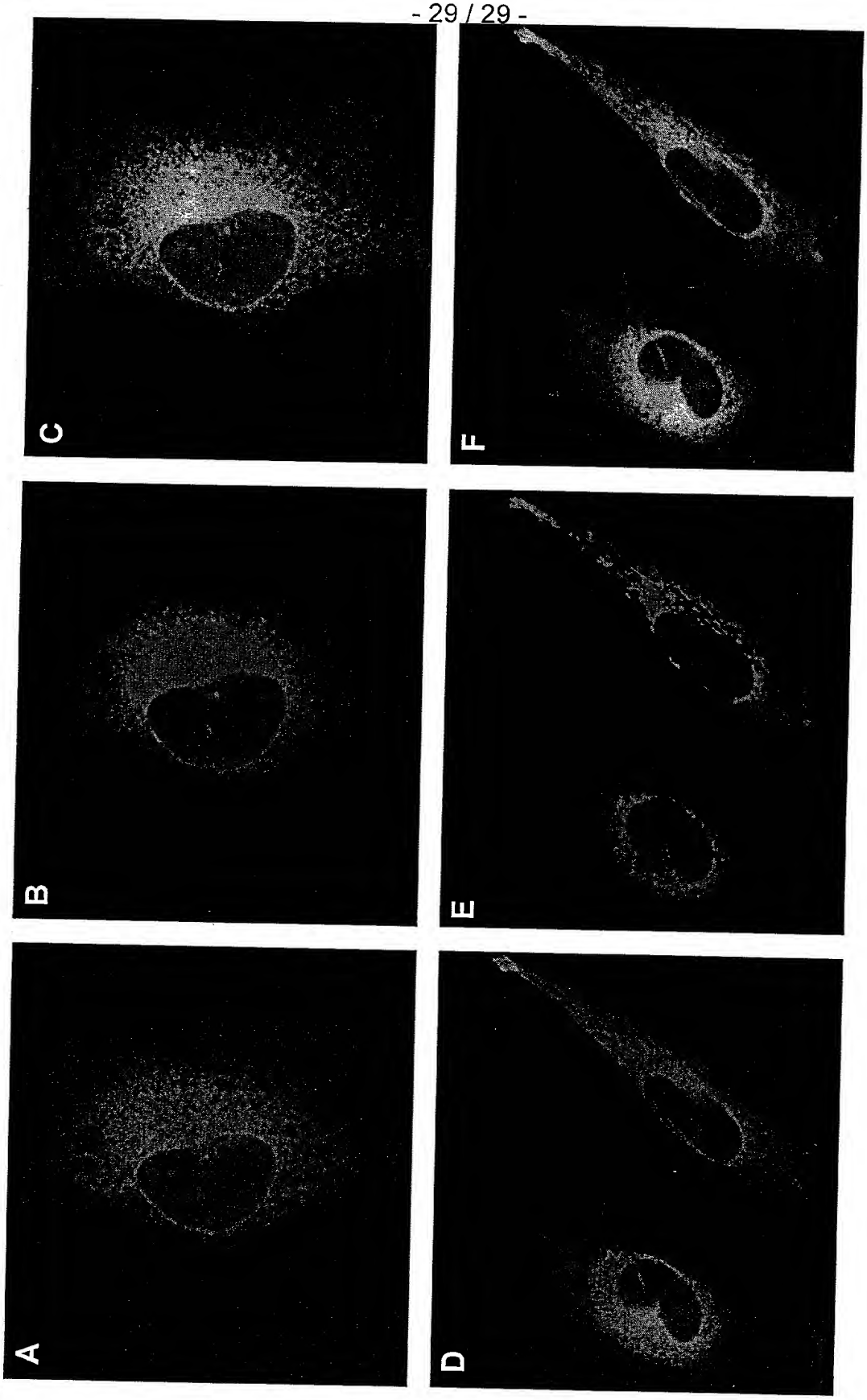


Fig. 21

DECLARATION AND POWER OF ATTORNEY U.S.A.

ALL PATENTS, INCLUDING DESIGN FOR APPLICATION BASED ON PCT; PARIS CONVENTION; NON PRIORITY; OR PROVISIONAL APPLICATIONS

FOR ATTORNEY'S DOCKET NO. NR. 1424

ATTORNEYS' DOCKET NO.

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or an additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

101 Methods of diagnosing or treating neurological diseases

102 which is described and claimed in:

☒ PCT International Application No. PCT/EP 99/08744 filed 12/11/1999

☐ the attached specification

☐ the specification in application Serial No. _____ filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

103 Prior Foreign Application(s)

(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed	
98 121 478.6	Europe	12/11/1998	☒ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No

104 I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. _____ Filing Date _____ Application No. _____ Filing Date _____

105 I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); ALLEN S. MELSER (27,215); MICHAEL R. SLOBASKY (28,421); JONATHAN L. SCHERER (29,851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409); YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

SEND CORRESPONDENCE TO: CUSTOMER NO. 00136 or JACOBSON, PRICE, HOLMAN & STERN PROFESSIONAL LIMITED LIABILITY COMPANY 400 SEVENTH STREET, N.W. WASHINGTON, D.C. 20004	DIRECT TELEPHONE CALLS TO: (please use Attorney's Docket No.) (202) 638-6666 JACOBSON, PRICE, HOLMAN & STERN PROFESSIONAL LIMITED LIABILITY COMPANY

Inventor(s) name must include at least one unabbreviated first or middle name.

201 FULL NAME OF INVENTOR	FAMILY NAME: Nitsch	GIVEN NAME: Roger	MIDDLE NAME:		
RESIDENCE & CITIZENSHIP	CITY: Zollikon CHX	STATE OR FOREIGN COUNTRY: Switzerland	COUNTRY OF CITIZENSHIP: Switzerland		
POST OFFICE ADDRESS	POST OFFICE ADDRESS: Gugger Str. 19	CITY: Zollikon	STATE OR COUNTRY: Switzerland	ZIP CODE: 8702	
202 FULL NAME OF INVENTOR	FAMILY NAME: Greeve	GIVEN NAME: Isabell	MIDDLE NAME:		
RESIDENCE & CITIZENSHIP	CITY: Hamburg DEX	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany		
POST OFFICE ADDRESS	POST OFFICE ADDRESS: Oberstrasse 108	CITY: Hamburg	STATE OR COUNTRY: Germany	ZIP CODE: 20143	
203 FULL NAME OF INVENTOR	FAMILY NAME:	GIVEN NAME:	MIDDLE NAME:		
RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:		
POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE OR COUNTRY:	ZIP CODE:	

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE April 15, 2001	DATE 04/04/01	DATE

☐ Additional inventors are named on separately numbered sheets attached hereto.

SEQUENCE LISTING

<110> NITSCH, ROGER
GREEVE, ISABELL

<120> METHODS OF DIAGNOSING OR TREATING NEUROLOGICAL DISEASES AND CELL DEGENERATION

<130> 10496/P66566US0

<140> 09/831,754
<141> 2001-05-14

<150> PCT/EP99/08744
<151> 1999-11-12

<150> 98 121 478.6
<151> 1998-11-12

<160> 10

<170> PatentIn Ver. 2.1

<210> 1
<211> 516
<212> PRT
<213> Homo sapiens

<400> 1

```
Met Glu Pro Ala Val Ser Leu Ala Val Cys Ala Leu Leu Phe Leu Leu
 1               5                  10                  15

Trp Val Arg Leu Lys Gly Leu Glu Phe Val Leu Ile His Gln Arg Trp
            20                  25                  30

Val Phe Val Cys Leu Phe Leu Leu Pro Leu Ser Leu Ile Phe Asp Ile
        35                  40                  45

Tyr Tyr Tyr Val Arg Ala Trp Val Val Phe Lys Leu Ser Ser Ala Pro
    50                  55                  60

Arg Leu His Glu Gln Arg Val Arg Asp Ile Gln Lys Gln Val Arg Glu
65                  70                  75                  80

Trp Lys Glu Gln Gly Ser Lys Thr Phe Met Cys Thr Gly Arg Pro Gly
                85                  90                  95

Trp Leu Thr Val Ser Leu Arg Val Gly Lys Tyr Lys Lys Thr His Lys
            100                 105                 110

Asn Ile Met Ile Asn Leu Met Asp Ile Leu Glu Val Asp Thr Lys Lys
        115                 120                 125

Gln Ile Val Arg Val Glu Pro Leu Val Thr Met Gly Gln Val Thr Ala
    130                 135                 140

Leu Leu Thr Ser Ile Gly Trp Thr Leu Pro Val Leu Pro Glu Leu Asp
145                 150                 155                 160
```

Asp Leu Thr Val Gly Gly Leu Ile Met Gly Thr Gly Ile Glu Ser Ser
165 170 175

Ser His Lys Tyr Gly Leu Phe Gln His Ile Cys Thr Ala Tyr Glu Leu
180 185 190

Val Leu Ala Asp Gly Ser Phe Val Arg Cys Thr Pro Ser Glu Asn Ser
195 200 205

Asp Leu Phe Tyr Ala Val Pro Trp Ser Cys Gly Thr Leu Gly Phe Leu
210 215 220

Val Ala Ala Glu Ile Arg Ile Ile Pro Ala Lys Lys Tyr Val Lys Leu
225 230 235 240

Arg Phe Glu Pro Val Arg Gly Leu Glu Ala Ile Cys Ala Lys Phe Thr
245 250 255

His Glu Ser Gln Arg Gln Glu Asn His Phe Val Glu Gly Leu Leu Tyr
260 265 270

Ser Leu Asp Glu Ala Val Ile Met Thr Gly Val Met Thr Asp Glu Ala
275 280 285

Glu Pro Ser Lys Leu Asn Ser Ile Gly Asn Tyr Tyr Lys Pro Trp Phe
290 295 300

Phe Lys His Val Glu Asn Tyr Leu Lys Thr Asn Arg Glu Gly Leu Glu
305 310 315 320

Tyr Ile Pro Leu Arg His Tyr Tyr His Arg His Thr Arg Ser Ile Phe
325 330 335

Trp Glu Leu Gln Asp Ile Ile Pro Phe Gly Asn Asn Pro Ile Phe Arg
340 345 350

Tyr Leu Phe Gly Trp Met Val Pro Pro Lys Ile Ser Leu Leu Lys Leu
355 360 365

Thr Gln Gly Glu Thr Leu Arg Lys Leu Tyr Glu Gln His His Val Val
370 375 380

Gln Asp Met Leu Val Pro Met Lys Cys Leu Gln Gln Ala Leu His Thr
385 390 395 400

Phe Gln Asn Asp Ile His Val Tyr Pro Ile Trp Leu Cys Pro Phe Ile
405 410 415

Leu Pro Ser Gln Pro Gly Leu Val His Pro Lys Gly Asn Glu Ala Glu
420 425 430

Leu Tyr Ile Asp Ile Gly Ala Tyr Gly Glu Pro Arg Val Lys His Phe
435 440 445

Glu Ala Arg Ser Cys Met Arg Gln Leu Glu Lys Phe Val Arg Ser Val
450 455 460

```
His Gly Phe Gln Met Leu Tyr Ala Asp Cys Tyr Met Asn Arg Glu Glu
465                 470                 475                 480

Phe Trp Glu Met Phe Asp Gly Ser Leu Tyr His Lys Leu Arg Glu Lys
                485                 490                 495

Leu Gly Cys Gln Asp Ala Phe Pro Glu Val Tyr Asp Lys Ile Cys Lys
            500                 505                 510

Ala Ala Arg His
        515
```

<210> 2
<211> 4248
<212> DNA
<213> Homo sapiens

<400> 2

```
cccgggctgt gggctacagg cgcagagcgg gccaggcgcg gagctggcgg cagtgacagg 60
aggcgcgaac ccgcagcgct taccgcgcgg cgccgcacca tggagcccgc cgtgtcgctg 120
gccgtgtgcg cgctgctctt cctgctgtgg gtgcgcctga aggggctgga gttcgtgctc 180
atccaccagc gctgggtgtt cgtgtgcctc ttcctcctgc cgctctcgct tatcttcgat 240
atctactact acgtgcgcgc ctgggtggtg ttcaagctca gcagcgctcc gcgcctgcac 300
gagcagcgcg tgcgggacat ccagaagcag gtgcgggaat ggaaggagca gggtagcaag 360
accttcatgt gcacggggcg ccctggctgg ctcactgtct cactacgtgt cgggaagtac 420
aagaagacac acaaaaacat catgatcaac ctgatggaca ttctggaagt ggacaccaag 480
aaacagattg tccgtgtgga gcccttggtg accatgggcc aggtgactgc cctgctgacc 540
tccattggct ggactctccc cgtgttgcct gagcttgatg acctcacagt ggggggcttg 600
atcatgggca caggcatcga gtcatcatcc cacaagtacg gcctgttcca acacatctgc 660
actgcttacg agctggtcct ggctgatggc agctttgtgc gatgcactcc gtccgaaaac 720
tcagacctgt tctatgccgt accctggtcc tgtgggacgc tgggtttcct ggtggccgct 780
gagatccgca tcatccctgc caagaagtac gtcaagctgc gtttcgagcc agtgcggggc 840
ctggaggcta tctgtgccaa gttcacccac gagtcccagc ggcaggagaa ccacttcgtg 900
gaagggctgc tctactccct ggatgaggct gtcattatga caggggtcat gacagatgag 960
gcagagccca gcaagctgaa tagcattggc aattactaca agccgtggtt ctttaagcat 1020
gtggagaact atctgaagac aaaccgagag ggcctggagt acattccctt gagacactac 1080
taccaccgcc acacgcgcag catcttctgg gagctccagg acatcatccc ctttggcaac 1140
aaccccatct tccgctacct ctttggctgg atggtgcctc ccaagatctc cctcctgaag 1200
ctgacccagg gtgagaccct gcgcaagctg tacgagcagc accacgtggt gcaggacatg 1260
ctggtgccca tgaagtgcct gcagcaggcc ctgcacacct tccaaaacga catccacgtc 1320
taccccatct ggctgtgtcc gttcatcctg cccagccagc caggcctagt gcaccccaaa 1380
ggaaatgagg cagagctcta catcgacatt ggagcatatg gggagccgcg tgtgaaacac 1440
tttgaagcca ggtcctgcat gaggcagctg gagaagtttg tccgcagcgt gcatggcttc 1500
cagatgctgt atgccgactg ctacatgaac cgggaggagt tctgggagat gtttgatggc 1560
tccttgtacc acaagctgcg agagaagctg ggttgccagg acgccttccc cgaggtgtac 1620
gacaagatct gcaaggccgc caggcactga gctggagccc gcctggagag acagacacgt 1680
gtgagtggtc aggcatcttc ccttcactca agcttggctg ctttcctaga tccacacttt 1740
caaagagaaa cccctccaga actcccaccc tgacagccca acaccacctt cctcctggct 1800
tccagggggc agcccagtgg aatggaaaga atgtgggatt tggagtcaga caagcctgag 1860
tccagttccc cgtttagaac tcattagctg tgtgactctg ggtgagtccc ttaacccctc 1920
tgagcccggg tctcttcatt agttgaaagg gatagtaata cctacttgca ggttgttgtc 1980
atctgagttg agcactggtc acattgaagg tgctgggtaa gtggtagctc ttgttgcttc 2040
ccgttcagcg tcacatctgc agtggagcct gaaaaggctc cacattaggt cacctgtgca 2100
cagccatggc tggaatgatg aaggggatac gctggagttg ccctgccatc gcctccatca 2160
gccagacgag gtcctcacag gagaaggaca gctcttcccc accctgggat ctcaggaggg 2220
cagccacgga gtggggaggc cccagatgcg ctgtgccaaa gccaggtccg aggccaaagt 2280
tctccctgcc atccttggtg ccgtcctgcc ccttcctcct tcatgcctgg gcctgcaggc 2340
```

ccaccccagc caccactgag tccactcgga gtgccctgtg ttcctggaga aggcattcca 2400
gggttgaatc ttgtcccagc ctcagcctgg gacacctagg tggagagagt ggtctccgct 2460
ctgaattgga tccaggggac ctgggctcat tcttcttggc tcaccaaccc tgcaggcctc 2520
atctttccca aaacccactt tgtcttggtg ggagtgggtc cgcgctgctc tgcagcaggg 2580
gctggggagt ggacagcatc aggtgggaaa gtggagtcca ccctcatgtt tctgtaggat 2640
tctcaccgtg gggctggaag aaaagagcat cgacttgatt tctccaacca ctcatccctc 2700
ttttctttc ttccaccact ccccacccca gctgtagtta atttcagtgc cttacaaatc 2760
ctaagctcag agaaagttcc atttccgttc cagagggaag ggaacctccc taggtccttc 2820
cctggcttgt tataacgcaa agcttggttg tttatgcaac tctatcttaa gaactgccca 2880
gcctcagctg aaaacccgaa tctgagaagg aattgcgtca tgtaagggaa gctggaatta 2940
agggagctga gccagtcatg gttgtggcgt gtgagtcagg agacctaggt ttcagcccct 3000
ctctactgtc agcgagctgt gcaacgtggg caagtcattg tcctctgagc tgcagtttcc 3060
tcatctgtca catcgctaca gacaagacct ccctggaacc cttctgattg tcttagacac 3120
tgtggttgca aaacccacgg aaagcctcat ttgtgtggaa agtcagagga aaaatgatcc 3180
agtggacact tggggattat ctgtcattca agatccttcc ttcaacccca aggccagctc 3240
ccatctcatt tccagaaagg ctcatacctg gcttgcaggg aagcatctgt cttgtcattc 3300
caggtgccag aatcctctca gagtcattga agggtgttca cccatcccac ccaaggcttg 3360
gcacactgcc agtgtcttag cagggtcttg tgagggctgg gggcatccag gcactcagaa 3420
ggcaaaggaa ccaccctacc catttggcct ctggaggggg cagaagaaag aaagaaacct 3480
catcctatat tttacaaagc atgtgaattc tggcattagc tctcatagga gacccatgtg 3540
cttccttgct cagtgcaaaa ctgatgattc tacttgctgt agatgaatgg ttaacacgag 3600
ctagttaaac agtgccattg ttttgccagt gaagcctcca accctaagcc actgggacgg 3660
tggccagaga tgccagcagc ctctgtcgcc cttagtcata taaccaaaat ccagacctta 3720
tccacaaccc ggggcttgga aaggaaggta ttttggaatc acaccctccg gttatgttgc 3780
tccagtaaaa tcttgcctgg aaagaggcag tcttcttagc atggtgagct gagttcatgg 3840
ctttttttg tagccagtcc tgtccctggc catccatgtg atggttttgg atggagttaa 3900
acttgatgcc agtgggcagt gcatgtggaa agtatcagag taagcctctc ccctccagag 3960
ccctgagttt cttggctgca tgaaggtttt ctttagaatc agaattgtag ccagtttctt 4020
tggccagaag gatgaatact tggatattac tgaaagggag gggtggagat gggtgtggca 4080
gtgtatggtg tgtgattttt attttcttct ttggtcatgg gggccaagga gaaaggcatg 4140
aatcttccct gtcaggctct tacagccaca ggcactgtgt ctactgtctg gaagacatgt 4200
ccccgtggct gtggggccgc tgcttctgtt taaataaaag tggcctgg 4248

<210> 3
<211> 4187
<212> DNA
<213> Homo sapiens

<400> 3
ggcgcgaacc cgcagcgctt accgcgcggc gccgcaccat ggagcccgcc gtgtcgctgg 60
ccgtgtgcgc gctgctcttc ctgctgtggg tgcgcctgaa ggggctggag ttcgtgctca 120
tccaccagcg ctgggtgttc gtgtgcctct tcctcctgcc gctctcgctt atcttcgata 180
tctactacta cgtgcgcgcc tgggtggtgt tcaagctcag cagcgctccg cgcctgcacg 240
agcagcgcgt gcgggacatc cagaagcagg tgcgggaatg gaaggagcag ggtagcaaga 300
ccttcatgtg cacggggcgc cctggctggc tcactgtctc actacgtgtc gggaagtaca 360
agaagacaca caaaaacatc atgatcaacc tgatggacat tctggaagtg gacaccaaga 420
aacagattgt ccgtgtggag cccttggtga ccatgggcca ggtgactgcc ctgctgacct 480
ccattggctg gactctcccc gtgttgcctg agcttgatga cctcacagtg gggggcttga 540
tcatgggcac aggcatcgag tcatcatccc acaagtacgg cctgttccaa cacatctgca 600
ctgcttacga gctggtcctg gctgatggca gctttgtgcg atgcactccg tccgaaaact 660
cagacctgtt ctatgccgta ccctggtcct gtgggacgct gggtttcctg gtggccgctg 720
agatccgcat catccctgcc aagaagtacg tcaagctgcg tttcgagcca gtgcgggggcc 780
tggaggctat ctgtgccaag ttcacccacg agtcccagcg gcaggagaac cacttcgtgg 840
aagggctgct ctactccctg gatgaggctg tcattatgac aggggtcatg acagatgagg 900
cagagcccag caagctgaat agcattggca attactacaa gccgtggttc tttaagcatg 960
tggagaacta tctgaagaca aaccgagagg gcctggagta cattcccttg agacactact 1020
accaccgcca cacgcgcagc atcttctggg agctccagga catcatcccc tttggcaaca 1080

accccatctt ccgctacctc tttggctgga tggtgcctcc caagatctcc ctcctgaagc 1140
tgacccaggg tgagaccctg cgcaagctgt acgagcagca ccacgtggtg caggacatgc 1200
tggtgcccat gaagtgcctg cagcaggccc tgcacacctt ccaaaacgac atccacgtct 1260
accccatctg gctgtgtccg ttcatcctgc ccagccagcc aggcctagtg caccccaaag 1320
gaaatgaggc agagctctac atcgacattg gagcatatgg ggagccgcgt gtgaaacact 1380
ttgaagccag gtcctgcatg aggcagctgg agaagtttgt ccgcagcgtg catggcttcc 1440
agatgctgta tgccgactgc tacatgaacc gggaggagtt ctgggagatg tttgatggct 1500
ccttgtacca caagctgcga gagaagctgg gttgccagga cgccttcccc gaggtgtacg 1560
acaagatctg caaggccgcc aggcactgag ctggagcccg cctggagaga cagacacgtg 1620
tgagtggtca ggcatcttcc cttcactcaa gcttggctgc tttcctagat ccacactttc 1680
aaagagaaac ccctccagaa ctcccaccct gacagcccaa caccaccttc ctcctggctt 1740
ccaggggcca gcccagtgga atggaaagaa tgtgggattt ggagtcagac aagcctgagt 1800
ccagttcccc gtttagaact cattagctgt gtgactctgg gtgagtccct taacccctct 1860
gagcccgggt ctcttcatta gttgaaaggg atagtaatac ctacttgcag gttgttgtca 1920
tctgagttga gcactggtca cattgaaggt gctgggtaag tggtagctct tgttgcttcc 1980
cgttcagcgt cacatctgca gtggagcctg aaaaggctcc acattaggtc acctgtgcac 2040
agccatggct ggaatgatga aggggatacg ctggagttgc cctgccatcg cctccatcag 2100
ccagacgagg tcctcacagg agaaggacag ctcttcccca ccctgggatc tcaggagggc 2160
agccacggag tggggaggcc ccagatgcgc tgtgccaaag ccaggtccga ggccaaagtt 2220
ctccctgcca tccttggtgc cgtcctgccc cttcctcctt catgcctggg cctgcaggcc 2280
caccccagcc accactgagt ccactcggag tgccctgtgt tcctggagaa ggcattccag 2340
ggttgaatct tgtcccagcc tcagcctggg acacctaggt ggagagagtg gtctccgctc 2400
tgaattggat ccaggggacc tgggctcatt cttcttggct caccaaccct gcaggcctca 2460
tctttcccaa aacccacttt gtcttggtgg gagtgggtcc gcgctgctct gcagcagggg 2520
ctggggagtg gacagcatca ggtgggaaag tggagtccac cctcatgttt ctgtaggatt 2580
ctcaccgtgg ggctggaaga aaagagcatc gacttgattt ctccaaccac tcatccctct 2640
ttttctttct tccaccactc cccaccccag ctgtagttaa tttcagtgcc ttacaaatcc 2700
taagctcaga gaaagttcca tttccgttcc agagggaagg gaacctccct aggtccttcc 2760
ctggcttgtt ataacgcaaa gcttggttgt ttatgcaact ctatcttaag aactgcccag 2820
cctcagctga aaacccgaat ctgagaagga attgcgtcat gtaagggaag ctggaattaa 2880
gggagctgag ccagtcatgg ttgtggcgtg tgagtcagga gacctaggtt tcagcccctc 2940
tctactgtca gcgagctgtg caacgtgggc aagtcattgt cctctgagct gcagtttcct 3000
catctgtcac atcgctacag acaagacctc cctggaaccc ttctgattgt cttagacact 3060
gtggttgcaa aacccacgga aagcctcatt tgtgtggaaa gtcagaggaa aaatgatcca 3120
gtggacactt ggggattatc tgtcattcaa gatccttcct tcaaccccaa ggccagctcc 3180
catctcattt ccagaaaggc tcatacctgg cttgcaggga agcatctgtc ttgtcattcc 3240
aggtgccaga atcctctcag agtcattgaa gggtgttcac ccatcccacc caaggcttgg 3300
cacactgcca gtgtcttagc agggtcttgt gagggctggg ggcatccagg cactcagaag 3360
gcaaaggaac caccctaccc atttggcctc tggagggggc agaagaaaga aagaaacctc 3420
atcctatatt ttacaaagca tgtgaattct ggcattagct ctcataggag acccatgtgc 3480
ttccttgctc agtgcaaaac tgatgattct acttgctgta gatgaatggt taacacgagc 3540
tagttaaaca gtgccattgt tttgccagtg aagcctccaa ccctaagcca ctgggacggt 3600
ggccagagat gccagcagcc tctgtcgccc ttagtcatat aaccaaaatc cagaccttat 3660
ccacaacccg gggcttggaa aggaaggtat tttggaatca caccctccgg ttatgttgct 3720
ccagtaaaat cttgcctgga aagaggcagt cttcttagca tggtgagctg agttcatggc 3780
tttttttgt agccagtcct gtccctggcc atccatgtga tggttttgga tggagttaaa 3840
cttgatgcca gtgggcagtg catgtggaaa gtatcagagt aagcctctcc cctccagagc 3900
cctgagtttc ttggctgcat gaaggttttc tttagaatca gaattgtagc cagtttcttt 3960
ggccagaagg atgaatactt ggatattact gaaagggagg ggtggagatg ggtgtggcag 4020
tgtatggtgt gtgattttta ttttcttctt tggtcatggg ggccaaggag aaaggcatga 4080
atcttccctg tcaggctctt acagccacag gcactgtgtc tactgtctgg aagacatgtc 4140
cccgtggctg tggggccgct gcttctgttt aaataaaagt ggcctgg 4187

<210> 4
<211> 4186
<212> DNA
<213> Homo sapiens

<400> 4
ggcgcgaacc cgcagcgctt accgcgcggc gccgcaccat ggagcccgcc gtgtcgctgg 60
ccgtgtgcgc gctgctcttc ctgctgtggg tgcgcctgaa ggggctggag ttcgtgctca 120
tccaccagcg ctgggtgttc gtgtgcctct tcctcctgcc gctctcgctt atcttcgata 180
tctactacta cgtgcgcgcc tgggtggtgt tcaagctcag cagcgctccg cgcctgcacg 240
agcagcgcgt gcgggacatc cagaagcagg tgcgggaatg gaaggagcag ggtagcaaga 300
ccttcatgtg cacggggcgc cctggctggc tcactgtctc actacgtgtc gggaagtaca 360
agaagacaca caaaaacatc atgatcaacc tgatggacat tctggaagtg gacaccaaga 420
aacagattgt ccgtgtggag ccccttggtga ccatgggcca ggtgactgcc ctgctgacct 480
ccattggctg gactctcccc gtgttgcctg agcttgatga cctcacagtg gggggcttga 540
tcatgggcac aggcatcgag tcatcatccc acaagtacgg cctgttccaa cacatctgca 600
ctgcttacga gctggtcctg gctgatggca gctttgtgcg atgcactccg tccgaaaact 660
cagacctgtt ctatgccgta ccctggtcct gtgggacgct gggtttcctg gtggccgctg 720
agatccgcat catccctgcc aagaagtacg tcaagctgcg tttcgagcca gtgcggggcc 780
tggaggctat ctgtgccaag ttcacccacg agtcccagcg gcaggagaac cacttcgtgg 840
aagggctgct ctactccctg gatgaggctg tcattatgac aggggtcatg acagatgagg 900
cagagcccag caagctgaat agcattggca attactacaa gccgtggttc tttaagcatg 960
tggagaacta tctgaagaca aaccgagagg gcctggagta cattcccttg agacactact 1020
accaccgcca cacgcgcagc atcttctggg agctccagga catcatcccc tttggcaaca 1080
accccatctt ccgctacctc tttggctgga tggtgcctcc caagatctcc ctcctgaagc 1140
tgacccaggg tgagaccctg cgcaagtgta cgagcagcac cacgtggtgc aggacatgct 1200
ggtgcccatg aagtgcctgc agcaggccct gcacaccttc caaaacgaca tccacgtcta 1260
ccccatctgg ctgtgtccgt tcatcctgcc cagccagcca ggcctagtgc accccaaagg 1320
aaatgaggca gagctctaca tcgacattgg agcatatggg gagccgcgtg tgaaacactt 1380
tgaagccagg tcctgcatga ggcagctgga gaagtttgtc cgcagcgtgc atggcttcca 1440
gatgctgtat gccgactgct acatgaaccg ggaggagttc tgggagatgt ttgatggctc 1500
cttgtaccac aagctgcgag agaagctggg ttgccaggac gccttccccg aggtgtacga 1560
caagatctgc aaggccgcca ggcactgagc tggagcccgc ctggagagac agacacgtgt 1620
gagtggtcag gcatcttccc ttcactcaag cttggctgct ttcctagatc cacactttca 1680
aagagaaacc cctccagaac tcccaccctg acagcccaac accaccttcc tcctggcttc 1740
caggggggcag cccagtggaa tggaaagaat gtgggatttg gagtcagaca agcctgagtc 1800
cagttccccg tttagaactc attagctgtg tgactctggg tgagtccctt aacccctctg 1860
agcccgggtc tcttcattag ttgaaaggga tagtaatacc tacttgcagg ttgttgtcat 1920
ctgagttgag cactggtcac attgaaggtg ctgggtaagt ggtagctctt gttgcttccc 1980
gttcagcgtc acatctgcag tggagcctga aaaggctcca cattaggtca cctgtgcaca 2040
gccatggctg gaatgatgaa ggggatacgc tggagttgcc ctgccatcgc ctccatcagc 2100
cagacgaggt cctcacagga gaaggacagc tcttccccac cctgggatct caggagggca 2160
gccacggagt ggggaggccc cagatgcgct gtgccaaagc caggtccgag gccaaagttc 2220
tccctgccat ccttggtgcc gtcctgcccc ttcctccttc atgcctgggc ctgcaggccc 2280
accccagcca ccactgagtc cactcggagt gccctgtgtt cctggagaag gcattccagg 2340
gttgaatctt gtcccagcct cagcctggga cacctaggtg gagagagtgg tctccgctct 2400
gaattggatc caggggacct gggctcattc ttcttggctc accaaccctg caggcctcat 2460
ctttcccaaa acccactttg tcttggtggg agtgggtccg cgctgctctg cagcaggggc 2520
tggggagtgg acagcatcag gtgggaaagt ggagtccacc ctcatgtttc tgtaggattc 2580
tcaccgtggg gctggaagaa aagagcatcg acttgatttc tccaaccact catccctctt 2640
tttctttctt ccaccactcc ccaccccagc tgtagttaat ttcagtgcct tacaaatcct 2700
aagctcagag aaagttccat ttccgttcca gagggaaggg aacctcccta ggtccttccc 2760
tggcttgtta taacgcaaag cttggttgtt tatgcaactc tatcttaaga actgcccagc 2820
ctcagctgaa aacccgaatc tgagaaggaa ttgcgtcatg taagggaagc tggaattaag 2880
ggagctgagc cagtcatggt tgtggcgtgt gagtcaggag acctaggttt cagcccctct 2940
ctactgtcag cgagctgtgc aacgtgggca agtcattgtc ctctgagctg cagtttcctc 3000
atctgtcaca tcgctacaga caagacctcc ctggaaccct tctgattgtc ttagacactg 3060
tggttgcaaa acccacggaa agcctcattt gtgtggaaag tcagaggaaa aatgatccag 3120
tggacacttg gggattatct gtcattcaag atccttcctt caaccccaag gccagctccc 3180
atctcatttc cagaaaggct catacctggc ttgcagggaa gcatctgtct tgtcattcca 3240
ggtgccagaa tcctctcaga gtcattgaag ggtgttcacc catcccaccc aaggcttggc 3300
acactgccag tgtcttagca gggtcttgtg agggctgggg gcatccaggc actcagaagg 3360

caaaggaacc accctaccca tttggcctct ggagggggca gaagaaagaa agaaacctca 3420
tcctatattt tacaaagcat gtgaattctg gcattagctc tcataggaga cccatgtgct 3480
tccttgctca gtgcaaaact gatgattcta cttgctgtag atgaatggtt aacacgagct 3540
agttaaacag tgccattgtt ttgccagtga agcctccaac cctaagccac tgggacggtg 3600
gccagagatg ccagcagcct ctgtcgccct tagtcatata accaaaatcc agaccttatc 3660
cacaacccgg ggcttggaaa ggaaggtatt ttggaatcac accctccggt tatgttgctc 3720
cagtaaaatc ttgcctggaa agaggcagtc ttcttagcat ggtgagctga gttcatggct 3780
tttttttgta gccagtcctg tccctggcca tccatgtgat ggttttggat ggagttaaac 3840
ttgatgccag tgggcagtgc atgtggaaag tatcagagta agcctctccc ctccagagcc 3900
ctgagtttct tggctgcatg aaggttttct ttagaatcag aattgtagcc agtttctttg 3960
gccagaagga tgaatacttg gatattactg aaagggaggg gtggagatgg gtgtggcagt 4020
gtatggtgtg tgatttttat tttcttcttt ggtcatgggg gccaaggaga aaggcatgaa 4080
tcttccctgt caggctctta cagccacagg cactgtgtct actgtctgga agacatgtcc 4140
ccgtggctgt ggggccgctg cttctgttta aataaaagtg gcctgg 4186

<210> 5
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 5
gcgcttaccg cgcggcgccg cacc 24

<210> 6
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 6
gaccagggta cggcatagaa cagg 24

<210> 7
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 7
agaagtacgt caagctgcgt ttcg 24

<210> 8
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 8
ttctctttga aagtgtggat ctag 24

<210> 9
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 9
tgccgaagct tggagctt 18

<210> 10
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 10
tgccgaagct ttggtcat 18

United States Patent & Trademark Office

Office of Initial Patent Examination -- Scanning Division

Application deficiencies found during scanning:

☐ Page(s)__________ of ____________________________ were not present for scanning.
(Document title)

☐ Page(s)__________ of ____________________________ were not present for scanning.
(Document title)

☑ ***Scanned copy is best available.*** Drawings, figures are very dark.